

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
 US Department of Commerce
 United States Patent and Trademark
 Office, PCT
 2011 South Clark Place Room
 CP2/5C24
 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE
 in its capacity as elected Office

Date of mailing (day/month/year) 08 June 2001 (08.06.01)	
International application No. PCT/JP00/06375	Applicant's or agent's file reference 2648WO0P
International filing date (day/month/year) 19 September 2000 (19.09.00)	Priority date (day/month/year) 20 September 1999 (20.09.99)
Applicant KATO, Kaneyoshi et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
 11 April 2001 (11.04.01)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not


made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Antonia Muller Telephone No.: (41-22) 338.83.38
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P C T

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving ● use only	
International Application No.	
International Filing Date	
Name of receiving Office and "PCT International Application"	
Applicant's or agent's file reference (if desired)(12 characters maximum) 2648WO0P	

Box No. I	TITLE OF INVENTION Melanin Concentrating Hormone Antagonist		
Box No. II	APPLICANT		
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> Takeda Chemical Industries, Ltd. 1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi, OSAKA 541-0045 JAPAN		<input type="checkbox"/> This person is also inventor. Telephone No. Facsimile No. Teleprinter No.	
State (that is, country) of nationality: Japan		State (that is, country) of residence: Japan	
This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input checked="" type="checkbox"/> all designated States except the United States of America <input type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box			
Box No. III	FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)		
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> KATO Kaneyoshi 2-40, Maruyamadai 2-chome, Kawanishi-shi, HYOGO 666-0152 JAPAN		This person is: <input type="checkbox"/> applicant only <input checked="" type="checkbox"/> applicant and inventor <input type="checkbox"/> inventor only <i>(If this check-box is marked, do not fill in below.)</i>	
State (that is, country) of nationality: Japan		State (that is, country) of residence: Japan	
This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input checked="" type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box			
<input checked="" type="checkbox"/> Further applicants and/or (further) inventors are indicated on a continuation sheet.			
Box No. IV	AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE		
The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: <input checked="" type="checkbox"/> agent <input type="checkbox"/> common representative			
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)</i> Patent Attorney, Registered No. 11404, TAKAHASHI Shuichi Patent Attorney, Registered No. 11045, UCHIYAMA Tsutomu c/o Osaka Plant of Takeda Chemical Industries, Ltd. 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka-shi, OSAKA 532-0024 JAPAN		Telephone No. <div style="text-align: center;">03-3278-2235</div> Facsimile No. <div style="text-align: center;">03-3278-2222</div> Teleprinter No.	
<input type="checkbox"/> Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.			

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

TERAUCHI Jun
3-5-204, Hachizuka 3-chome, Ikeda-shi,
OSAKA 563-0024 JAPAN

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality: Japan

State (that is, country) of residence: Japan

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

MORI Masaaki
7-9-702, Kasuga 1-chome, Tsukuba-shi, IBARAKI
305-0821 JAPAN

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality: Japan

State (that is, country) of residence: Japan

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

SUZUKI Nobuhiro
1077-50, Oaza-yatabe, Tsukuba-shi, IBARAKI
305-0861 JAPAN

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality: Japan

State (that is, country) of residence: Japan

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

SHIMOMURA Yukio
12-1-410, Matsushiro 3-chome, Tsukuba-shi, IBARAKI
305-0035 JAPAN

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality: Japan

State (that is, country) of residence: Japan

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

TAKEKAWA Shiro
5-3-B305, Umezono 2-chome, Tsukuba-shi,
IBARAKI 305-0045 JAPAN

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality: Japan

State (that is, country) of residence: Japan

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

ISHIHARA Yuji
12-30-305, Ninomiya 1-chome, Tsukuba-shi, IBARAKI
305-0051 JAPAN

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality: Japan

State (that is, country) of residence: Japan

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; *at least one must be marked*):

Regional Patent

- ☒ AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | |
|---|--|
| <input checked="" type="checkbox"/> AB United Arab Emirates. | <input checked="" type="checkbox"/> LR Liberia |
| <input checked="" type="checkbox"/> AL Albania | <input type="checkbox"/> LS Lesotho |
| <input checked="" type="checkbox"/> AM Armenia | <input checked="" type="checkbox"/> LT Lithuania |
| <input type="checkbox"/> AT Austria | <input type="checkbox"/> LU Luxembourg |
| <input checked="" type="checkbox"/> AU Australia | <input checked="" type="checkbox"/> LV Latvia |
| <input checked="" type="checkbox"/> AZ Azerbaijan | <input checked="" type="checkbox"/> MA Morocco |
| <input checked="" type="checkbox"/> BA Bosnia and Herzegovina | <input checked="" type="checkbox"/> MD Republic of Moldova |
| <input checked="" type="checkbox"/> BB Barbados | <input checked="" type="checkbox"/> MG Madagascar |
| <input checked="" type="checkbox"/> BG Bulgaria | <input checked="" type="checkbox"/> MK The former Yugoslav Republic of Macedonia |
| <input checked="" type="checkbox"/> BR Brazil | <input checked="" type="checkbox"/> MN Mongolia |
| <input checked="" type="checkbox"/> BY Belarus | <input type="checkbox"/> MW Malawi |
| <input checked="" type="checkbox"/> CA Canada | <input checked="" type="checkbox"/> MX Mexico |
| <input type="checkbox"/> CH and LI Switzerland and Liechtenstein | <input checked="" type="checkbox"/> NO Norway |
| <input checked="" type="checkbox"/> CN China | <input checked="" type="checkbox"/> NZ New Zealand |
| <input checked="" type="checkbox"/> CR Costa Rica | <input checked="" type="checkbox"/> PL Poland |
| <input checked="" type="checkbox"/> CU Cuba | <input type="checkbox"/> PT Portugal |
| <input checked="" type="checkbox"/> CZ Czech Republic | <input checked="" type="checkbox"/> RO Romania |
| <input type="checkbox"/> DE Germany | <input checked="" type="checkbox"/> RU Russian Federation |
| <input type="checkbox"/> DK Denmark | <input type="checkbox"/> SD Sudan |
| <input type="checkbox"/> DM Dominica | <input type="checkbox"/> SE Sweden |
| <input checked="" type="checkbox"/> EE Estonia | <input checked="" type="checkbox"/> SG Singapore |
| <input type="checkbox"/> ES Spain | <input checked="" type="checkbox"/> SI Slovenia |
| <input type="checkbox"/> FI Finland | <input checked="" type="checkbox"/> SK Slovakia |
| <input type="checkbox"/> GB United Kingdom | <input type="checkbox"/> SL Sierra Leone |
| <input checked="" type="checkbox"/> GD Grenada | <input checked="" type="checkbox"/> TJ Tajikistan |
| <input checked="" type="checkbox"/> GE Georgia | <input checked="" type="checkbox"/> TM Turkmenistan |
| <input type="checkbox"/> GH Ghana | <input checked="" type="checkbox"/> TR Turkey |
| <input type="checkbox"/> GM Gambia | <input checked="" type="checkbox"/> TT Trinidad and Tobago |
| <input checked="" type="checkbox"/> HR Croatia | <input type="checkbox"/> TZ United Republic of Tanzania |
| <input checked="" type="checkbox"/> HU Hungary | <input checked="" type="checkbox"/> UA Ukraine |
| <input checked="" type="checkbox"/> ID Indonesia | <input type="checkbox"/> UG Uganda |
| <input checked="" type="checkbox"/> IL Israel | <input checked="" type="checkbox"/> US United States of America |
| <input checked="" type="checkbox"/> IN India | <input checked="" type="checkbox"/> UZ Uzbekistan |
| <input checked="" type="checkbox"/> IS Iceland | <input checked="" type="checkbox"/> VN Viet Nam |
| <input checked="" type="checkbox"/> JP Japan | <input checked="" type="checkbox"/> YU Yugoslavia |
| <input type="checkbox"/> KE Kenya | <input checked="" type="checkbox"/> ZA South Africa |
| <input checked="" type="checkbox"/> KG Kyrgyzstan | <input type="checkbox"/> ZW Zimbabwe |
| <input type="checkbox"/> KP Democratic People's Republic of Korea | |
| <input checked="" type="checkbox"/> KR Republic of Korea | |
| <input checked="" type="checkbox"/> KZ Kazakhstan | |
| <input checked="" type="checkbox"/> LC Saint Lucia | |
| <input checked="" type="checkbox"/> LK Sri Lanka | |

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet:

- ☒ DZ Democratic People's Republic of Algeria
☒ AG Antigua and Barbuda ☒ MZ Mozambique
☒ BZ Belize

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except the designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

Box No. VI PRIORITY CLAIM		<input type="checkbox"/> Further priority claims are indicated in the Supplemental Box		
Filing Date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application: * regional Office	international application: receiving Office
item(1) 20.09.99	Patent Application 11-266298	Japan		
item(2) 16.12.99	Patent Application 11-357889	Japan		
item(3) 20.04.00	Patent Application 2000-126272	Japan		

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s): (1), (2), (3)

* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA)
(If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):

Date (day/month/year) Number Country(or regional Office)

ISA / E P

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following number of sheets:

request : 5
description (excluding sequence listing part) : 335
claims : 16
abstract : 1
drawings : 0
sequence listing part of description : 11
Total number of sheets : 368

This international application is accompanied by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☒ separate signed power of attorney
3. ☒ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ other (specify):

Figure of the drawings which should accompany the abstract:

Language of filing of the international application:

English

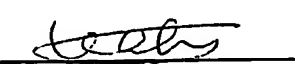
Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

TAKAHASHI Shuichi

UCHIYAMA Tsutomu


Shuichi TAKAHASHI


Tsutomu UCHIYAMA

For receiving Office use		2. Drawings: <input type="checkbox"/> received: <input type="checkbox"/> not received:
1. Date of actual receipt of the purported international application:		
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:		
4. Date of timely receipt of the required corrections under PCT Article 11(2):		
5. International Searching Authority (if two or more are competent): ISA/E P	6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid	

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

PATENT COOPERATION TREATY

7

PCT



From the INTERNATIONAL BUREAU

NOTIFICATION OF RECEIPT OF
RECORD COPY

(PCT Rule 24.2(a))

T :

TAKAHASHI, Shuichi
Osaka Plant of Takeda Chemical
Industries, Ltd.
17-85, Jusohonmachi 2-chome
Yodogawa-ku
Osaka-shi
Osaka 532-0024
JAPON


Date of mailing (day/month/year) 17 October 2000 (17.10.00)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 2648WO0P	International application No. PCT/JP00/06375

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

TAKEDA CHEMICAL INDUSTRIES, LTD. (for all designated States except US)
KATO, Kaneyoshi et al (for US)

International filing date	:	19 September 2000 (19.09.00)
Priority date(s) claimed	:	20 September 1999 (20.09.99) 16 December 1999 (16.12.99) 20 April 2000 (20.04.00)

Date of receipt of the record copy by the International Bureau	:	03 October 2000 (03.10.00)
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List of designated Offices

AP : GH,GM,KE,LS,MW,MZ,SD,SL,SZ,TZ,UG,ZW
EA : AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
EP : AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
OA : BF,BJ,CF,CG,CI,CM,GA,GN,GW,ML,MR,NE,SN,TD,TG
National : AE,AG,AL,AM,AU,AZ,BA,BB,BG,BR,BY,BZ,CA,CN,CR,CU,CZ,DM,DZ,EE,GD,GE,HR,HU,
ID,IL,IN,IS,JP,KG,KR,KZ,LC,LK,LR,LT,LV,MA,MD,MG,MK,MN,MX,MZ,NO,NZ,PL,RO,RU,SG,SI,
SK,TJ,TM,TR,TT,UA,US,UZ,VN,YU,ZA

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer:

Shinji IGARASHI

Facsimile No. (41-22) 740.14.35

Telephone No. (41-22) 338.83.38



Continuation of Form PCT/IB/301

NOTIFICATION OF RECEIPT OF RECORD COPY

Date of mailing (day/month/year) 17 October 2000 (17.10.00)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 2648WOOP	International application No. PCT/JP00/06375

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

- ☒ time limits for entry into the national phase
- ☒ confirmation of precautionary designations
- ☒ requirements regarding priority documents

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.



INFORMATION ON TIME LIMITS FOR ENTERING THE NATIONAL PHASE

The applicant is reminded that the "national phase" must be entered before each of the designated Offices indicated in the Notification of Receipt of Record Copy (Form PCT/IB/301) by paying national fees and furnishing translations, as prescribed by the applicable national laws.

The time limit for performing these procedural acts is **20 MONTHS** from the priority date or, for those designated States which the applicant elects in a demand for international preliminary examination or in a later election, **30 MONTHS** from the priority date, provided that the election is made before the expiration of 19 months from the priority date. Some designated (or elected) Offices have fixed time limits which expire even later than 20 or 30 months from the priority date. In other Offices an extension of time or grace period, in some cases upon payment of an additional fee, is available.

In addition to these procedural acts, the applicant may also have to comply with other special requirements applicable in certain Offices. It is the applicant's responsibility to ensure that the necessary steps to enter the national phase are taken in a timely fashion. Most designated Offices do not issue reminders to applicants in connection with the entry into the national phase.

For detailed information about the procedural acts to be performed to enter the national phase before each designated Office, the applicable time limits and possible extensions of time or grace periods, and any other requirements, see the relevant Chapters of Volume II of the PCT Applicant's Guide. Information about the requirements for filing a demand for international preliminary examination is set out in Chapter IX of Volume I of the PCT Applicant's Guide.

GR and ES became bound by PCT Chapter II on 7 September 1996 and 6 September 1997, respectively, and may, therefore, be elected in a demand or a later election filed on or after 7 September 1996 and 6 September 1997, respectively, regardless of the filing date of the international application. (See second paragraph above.)

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

CONFIRMATION OF PRECAUTIONARY DESIGNATIONS

This notification lists only specific designations made under Rule 4.9(a) in the request. It is important to check that these designations are correct. Errors in designations can be corrected where precautionary designations have been made under Rule 4.9(b). The applicant is hereby reminded that any precautionary designations may be confirmed according to Rule 4.9(c) before the expiration of 15 months from the priority date. If it is not confirmed, it will automatically be regarded as withdrawn by the applicant. There will be no reminder and no invitation. Confirmation of a designation consists of the filing of a notice specifying the designated State concerned (with an indication of the kind of protection or treatment desired) and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.

REQUIREMENTS REGARDING PRIORITY DOCUMENTS

For applicants who have not yet complied with the requirements regarding priority documents, the following is recalled.

Where the priority of an earlier national, regional or international application is claimed, the applicant must submit a copy of the said earlier application, certified by the authority with which it was filed ("the priority document") to the receiving Office (which will transmit it to the International Bureau) or directly to the International Bureau, before the expiration of 16 months from the priority date, provided that any such priority document may still be submitted to the International Bureau before that date of international publication of the international application, in which case that document will be considered to have been received by the International Bureau on the last day of the 16-month time limit (Rule 17.1(a)).

Where the priority document is issued by the receiving Office, the applicant may, instead of submitting the priority document, request the receiving Office to prepare and transmit the priority document to the International Bureau. Such request must be made before the expiration of the 16-month time limit and may be subjected by the receiving Office to the payment of a fee (Rule 17.1(b)).

If the priority document concerned is not submitted to the International Bureau or if the request to the receiving Office to prepare and transmit the priority document has not been made (and the corresponding fee, if any, paid) within the applicable time limit indicated under the preceding paragraphs, any designated State may disregard the priority claim, provided that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity to furnish the priority document within a time limit which is reasonable under the circumstances.

Where several priorities are claimed, the priority date to be considered for the purposes of computing the 16-month time limit is the filing date of the earliest application whose priority is claimed.



担当者	G·M	Pat·M	部長
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PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

TAKAHASHI, Shuichi
Osaka Plant of Takeda Chemical
Industries, Ltd.
17-85, Jusohonmachi 2-chome
Yodogawa-ku
Osaka-shi
Osaka 532-0024
JAPON

受付

'00.11.28

知的財産部

Date of mailing (day/month/year) 17 November 2000 (17.11.00)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 2648WOOP	
International application No. PCT/JP00/06375	
International publication date (day/month/year) Not yet published	
International filing date (day/month/year) 19 September 2000 (19.09.00)	Priority date (day/month/year) 20 September 1999 (20.09.99)
Applicant TAKEDA CHEMICAL INDUSTRIES, LTD. et al	

- The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
- An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

<u>Priority date</u>	<u>Priority application No.</u>	<u>Country or regional Office or PCT receiving Office</u>	<u>Date of receipt of priority document</u>
20 Sept 1999 (20.09.99)	11/266298	JP	06 Nove 2000 (06.11.00)
16 Dece 1999 (16.12.99)	11/357889	JP	06 Nove 2000 (06.11.00)
20 Apri 2000 (20.04.00)	2000/126272	JP	06 Nove 2000 (06.11.00)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 740.14.35	Authorized officer Magda BOUACHA Telephone No. (41-22) 338.83.38
--	--



PATENT COOPERATION TREATY

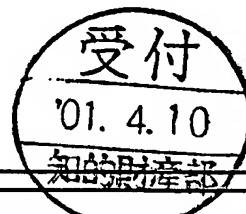
担当者	G·M	部長
(印)	(印)	

PCT

From the INTERNATIONAL BUREAU

To:

TAKAHASHI, Shuichi
Osaka Plant of Takeda Chemical
Industries, Ltd.
17-85, Jusohonmachi 2-chome
Yodogawa-ku
Osaka-shi
Osaka 532-0024
JAPON



NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

Date of mailing (day/month/year) 29 March 2001 (29.03.01)		
Applicant's or agent's file reference 2648WOOP		
IMPORTANT NOTICE		
International application No. PCT/JP00/06375	International filing date (day/month/year) 19 September 2000 (19.09.00)	Priority date (day/month/year) 20 September 1999 (20.09.99)
Applicant TAKEDA CHEMICAL INDUSTRIES, LTD. et al		

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:

AU, KR, US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE, AG, AL, AM, AP, AZ, BA, BB, BG, BR, BY, BZ, CA, CN, CR, CU, CZ, DM, DZ, EA, EE, EP, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KZ, LC, LK, LR, LT, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, OA, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, UZ, VN, YU, ZA

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on 29 March 2001 (29.03.01) under No. WO 01/21577

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

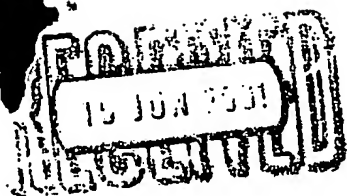
If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer J. Zahra
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38



PATENT COOPERATION TREATY



PCT

From the INTERNATIONAL BUREAU

INFORMATION CONCERNING ELECTED
OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

To:

CAFFIN, Lee
Takeda Euro Patent Office
Savannah House
11-12 Charles II Street
London SW1Y 4QU
ROYAUME-UNI

Date of mailing (day/month/year) 08 June 2001 (08.06.01)		
Applicant's or agent's file reference 2648WO0P		IMPORTANT INFORMATION
International application No. PCT/JP00/06375	International filing date (day/month/year) 19 September 2000 (19.09.00)	
		Priority date (day/month/year) 20 September 1999 (20.09.99)
Applicant TAKEDA CHEMICAL INDUSTRIES, LTD. et al		

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

EP : AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
National : AU, BG, CA, CN, CZ, IL, JP, KR, MN, NO, NZ, PL, RO, RU, SK, US


2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

AP : GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW
EA : AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
OA : BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
National : AE, AG, AL, AM, AZ, BA, BB, BR, BY, BZ, CR, CU, DM, DZ, EE, GD, GE, HR, HU, ID, IN, IS, KG, KZ, LC, LK, LR, LT, LV, MA, MD, MG, MK, MX, MZ, SG, SI, TJ, TM, TR, TT, UA, UZ, VN, YU, ZA

3. The applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing, if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

The entry into the European regional phase is postponed until 31 months from the priority date for all States designated for the purposes of obtaining a European patent.

The International Bureau of WIPO 34, chemin des C. lombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 740.14.35	Authorized officer: Antonia Muller  Telephone No. (41-22) 338.83.38
---	--

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 2648WOOP	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/JP 00/ 06375	International filing date (day/month/year) 19/09/2000	(Earliest) Priority Date (day/month/year) 20/09/1999
Applicant TAKEDA CHEMICAL INDUSTRIES, LTD.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

4. With regard to the title,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the abstract,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.



as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures.



INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 00/06375

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 35 and 36 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-33(partly), 35-38(partly)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.



FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-33(partly), 35-38(partly)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty (attention is drawn to the fact that claim 1 as it is drafted has to be considered purely as a compound claim). So many documents were retrieved (a few have been cited as a mere random selection) that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search has been restricted to:

compounds to formula I' (see claim 18) with $X = C(O)N$, $Y = -(CH_2)_2-$ whereby the substituents $A1-X-$ and $YNR1R2$ may not be attached in alpha-position to the C-atoms shared by the condensed ring (Ar'). Ar' , Ar and $R1/R2$ are as defined in claim 18.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.



PCT/JP 00/06375

IPC 7 C07C235/42 C07D235/84 C07D209/48 C07C237/40 C07C275/42
C07C233/44 A61K31/16 A61K31/40

IPC 7 C07C C07D

CHEM ABS Data, WPI Data, EPO-Internal, BEILSTEIN Data

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 32967 A (SMITHKLINE BEECHAM PLC ;HAM PETER (GB); GASTER LARAMIE MARY (GB);) 7 December 1995 (1995-12-07) cited in the application claims; examples ---	1-5,7, 13-16
X	WO 98 38156 A (KATO KANEYOSHI ;TERAUCHI JUN (JP); FUKUMOTO HIROAKI (JP); KAKIHANA) 3 September 1998 (1998-09-03) claims; examples ---	1-7,9-16
X	WO 99 01127 A (BONDINELL WILLIAM E ;SMITHKLINE BEECHAM CORP (US); CHAN JAMES A (U) 14 January 1999 (1999-01-14) claim 4; examples ---	1-7, 9-16,18, 29,32
	--- -/--	

☒ Patent family members are listed in annex.

"&" document member of the same patent family

15 JUL 68

Seufert, G



INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 00/06375

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 21 08 185 A (TROPONWERKE DINKLAGE & CO.) 7 September 1972 (1972-09-07) claims; examples ---	1-4, 8-16,18, 28,32
X	DE 24 48 257 A (TROPONWERKE DINKLAGE & CO) 22 April 1976 (1976-04-22) claims; examples ---	1-4,8-16
X	DE 25 02 588 A (TROPONWERKE DINKLAGE & CO) 29 July 1976 (1976-07-29) claims; examples ---	1-4,8-16
X	R. E. MEWSHAW ET AL.: "New Generation Dopaminergic Agents. 1. Discovery of a Novel Scaffold Which Embraces the D2 Agonist Pharmacophore. Structure-Activity Relationship of a Series of 2-(Aminomethyl)chromans" J. MED. CHEM., vol. 40, no. 26, 1997, pages 4235-56, XP002155829 * page 4248, right column, example 22b - page 4249, left column, example 39a * ---	1-4,7,9, 11-13
X	A. M. BIRCH ET AL.: "N-Substituted (2,3-Dihydro-1,4-benzodioxin-2-yl)methylamine Derivatives as D2 Antagonists/5-HT1A Partial Agonists with Potential as Atypical Antipsychotic Agents" J. MED. CHEM., vol. 42, no. 17, 1999, pages 3342-55, XP002155830 * scheme 8 compound 49 * ---	1-4,7,9, 11-13
X	DATABASE BEILSTEIN [Online] Beilstein Informationssysteme; XP002155831 * see BRN 5345411 * & J. CHEM. SOC. PERKIN TRANS. 1, vol. 5, 1992, pages 531-32, ---	1-4,7,9, 11-13
X	EP 0 533 266 A (GLAXO GROUP LTD) 24 March 1993 (1993-03-24) cited in the application claims; examples ---	1,4,5,7, 9,10, 13-16
X	WO 96 35671 A (DOW ROBERT L ;PFIZER (US)) 14 November 1996 (1996-11-14) cited in the application claims; examples ---	1,4,7, 13-16, 36,38

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 00/06375

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 920 864 A (PFIZER PROD INC) 9 June 1999 (1999-06-09) * page 3, line 10-14, 30-36; claims; examples *	1,4,7, 13-17, 35-38
A	--- QU D ET AL: "A ROLE FOR MELANIN-CONCENTRATING HORMONE IN THE CENTRAL REGULATION OF FEEDING BEHAVIOUR" NATURE,GB,MACMILLAN JOURNALS LTD. LONDON, vol. 380, 21 March 1996 (1996-03-21), pages 243-247, XP002037981 ISSN: 0028-0836 the whole document -----	1-38

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 00/06375

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9532967	A	07-12-1995	AU 2565595 A EP 0763034 A JP 10500960 T US 5756496 A ZA 9504330 A	21-12-1995 19-03-1997 27-01-1998 26-05-1998 17-05-1996
WO 9838156	A	03-09-1998	AU 6116698 A EP 0971878 A JP 11080098 A	18-09-1998 19-01-2000 23-03-1999
WO 9901127	A	14-01-1999	AU 8381398 A BR 9810758 A CN 1261795 T EP 1001766 A NO 996490 A ZA 9805542 A	25-01-1999 15-08-2000 02-08-2000 24-05-2000 27-12-1999 07-04-1999
DE 2108185	A	07-09-1972	AT 312593 B AT 308090 B AU 459412 B AU 3108771 A BE 769959 A CA 960669 A CH 563385 A CH 563386 A CH 564006 A CH 563384 A CS 172355 B DK 125919 B ES 393295 A FI 54117 B FR 2100927 A GB 1323179 A IL 37284 A NL 7109845 A OA 3762 A RO 59060 A SE 379541 B SU 402211 A SU 404237 A SU 461494 A SU 433678 A US 3897426 A US 3930003 A YU 184271 A,B	15-12-1973 15-05-1973 27-03-1975 18-01-1973 13-01-1972 07-01-1975 30-06-1975 30-06-1975 15-07-1975 30-06-1975 29-12-1976 21-05-1973 01-03-1975 30-06-1978 24-03-1972 11-07-1973 22-10-1974 19-01-1972 24-12-1971 15-01-1976 13-10-1975 12-10-1973 26-10-1973 25-02-1975 25-06-1974 29-07-1975 30-12-1975 10-07-1979
DE 2448257	A	22-04-1976	NONE	
DE 2502588	A	29-07-1976	NONE	
EP 0533266	A	24-03-1993	AU 2452992 A CA 2078506 A CN 1071922 A CZ 9202855 A FI 924159 A HU 66319 A JP 6107649 A MX 9205279 A	25-03-1993 19-03-1993 12-05-1993 14-04-1993 19-03-1993 28-11-1994 19-04-1994 01-03-1993

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 00/06375

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0533266 A		NO 923617 A	19-03-1993
		PL 295961 A	06-09-1993
		US 5356893 A	18-10-1994
		ZA 9207107 A	08-09-1993

WO 9635671 A	14-11-1996	CA 2220399 A	14-11-1996
		HU 9601240 A	29-09-1997
		AU 4747599 A	02-12-1999
		AU 706235 B	10-06-1999
		AU 5218596 A	21-11-1996
		BR 9602209 A	07-04-1998
		CZ 9601321 A	12-03-1997
		EP 0824519 A	25-02-1998
		FI 974172 A	07-11-1997
		JP 11504649 T	27-04-1999
		KR 190259 B	01-06-1999
		NO 961887 A	11-11-1996
		NZ 286548 A	25-03-1998
		PL 314120 A	12-11-1996
		SG 43365 A	17-10-1997
		TR 960980 A	21-11-1996
		US 5977124 A	02-11-1999

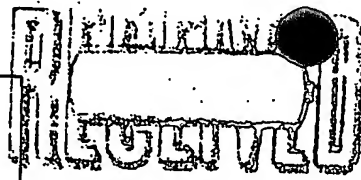
EP 0920864 A	09-06-1999	AU 9605598 A	24-06-1999
		HU 9802795 A	30-08-1999
		JP 11228447 A	24-08-1999



PATENT COOPERATION TREATY

9.10.01 ✓

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY



PCT

To:

CAFFIN, Lee
Takeda Euro Patent Office
Savannah House
11-12 Charles II Street
London SW1Y 4QU
GRANDE BRETAGNE

WRITTEN OPINION

(PCT Rule 66)

Date of mailing
(day/month/year) 09.07.2001

Applicant's or agent's file reference
2648WO0P

REPLY DUE within 3 month(s)
from the above date of mailing

International application No.
PCT/JP00/06375

International filing date (day/month/year)
19/09/2000

Priority date (day/month/year)
20/09/1999

International Patent Classification (IPC) or both national classification and IPC
C07C235/00

Applicant

TAKEDA CHEMICAL INDUSTRIES, LTD. et al.

1. This written opinion is the first drawn up by this International Preliminary Examining Authority.
2. This opinion contains indications relating to the following items:
 - I ☒ Basis of the opinion
 - II ☐ Priority
 - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - IV ☐ Lack of unity of invention
 - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - VI ☐ Certain document cited
 - VII ☒ Certain defects in the international application
 - VIII ☒ Certain observations on the international application
3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.
4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 20/01/2002.

Name and mailing address of the international preliminary examining authority:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer / Examiner

Seufert, G

Formalities officer (incl. extension of time limits)

Roche, S

Telephone No. +49 89 2399 8031





I. Basis of the opinion

1. With regard to the elements of the international application (Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"):

Description, pages:

1-335 as originally filed

Claims, No.:

1-38 as originally filed

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:



5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

- ☐ the entire international application,
☒ claims Nos. 1-33 (partly), 35-38(partly) ,

because:

- ☒ the said international application, or the said claims Nos. 35, 36 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the said claims Nos. 1-33 (partly), 35-38 (partly).

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-18, 28, 29, 32, 35-38
Inventive step (IS)	Claims	1-38
Industrial applicability (IA)	Claims	



2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet



Reference is made to the following documents:

- D1 WO-A-9901127
- D2 DE-A-2108185
- D3 WO-A-9532967
- D4 WO-A-9838156
- D5 DE-A-2448257
- D6 De-A-2502588
- D7 J. Med. Chem. 40(26), 1997, 4235-56
- D8 J. Med. Chem. 42(17), 1999, 3342-55
- D9 Beilstein Database, BRN 5345411 & J. Chem. Soc. Perkin Trans 1, 5, 1992, 531-2
- D10 EP-A-533266
- D11 WO-A-9635671
- D12 EP-A-920864
- D13 Nature, 380, 1996, 243-47

III. Non establishment of opinion

According to Rule 66.1e the International Preliminary Examination Authority is not required to carry out an examination on subject-matter for which no search report as been established.

The applicant has been informed by the Search Authority that a meaningful search has not been possible considering the large amount of documents relevant to the issue of novelty. The search has been restricted to the group of compounds as defined on the supplementary sheet included in the search report.

Consequently, a complete examination with regard to novelty, inventive step and industrial applicability has only been carried out for that group of compounds.

Claims 35 and 36 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).



V. Reasoned statement under Rule 66(2)(a)(ii) PCT with regard to novelty, inventive step and industrial applicability

Novelty

1. Claim 18 refers to compounds of the general formula (I) and claim 28 and 29 to subgroups of said general formula. Documents D1 and D2 anticipate compounds falling within the scope of claims 18, 28 and 29 (see D1, claim 4 and D2, claims and examples) and their pharmaceutical use. Therefore, claims 18, 28 and 29 as well as claim 32 are not considered to meet the requirement of Art. 33(2) PCT.
2. As mentioned above, the search has been restricted to a certain group of compounds according to claim 18 and only for those, the examination may be considered complete. However, with regard to the documents mentioned in the search report some preliminary remarks with regard to novelty of the rest of the subject-matter can be made.
 - 2.1 Although the subject-matter of claim 1 has not been searched completely, it is obvious that compounds of the general formula I are by no means new, (see documents D1-D12). Claim 1 is thereby considered as a claim referring to a compound of the formula (I). The expression "a melanin-concentrating hormone antagonist" is not considered to be limiting. Thus, claim 1 and the dependent claims 2-13 are not considered to meet the requirement of Art. 33(2) PCT.
 - 2.2 Similarly claims 14-16 are not considered to meet the requirements of Art. 33(2) PCT. A first medical use claim (i.e. "a compound for treating...") is only considered to be novel if the compounds are not known for any pharmaceutical activity. However, compounds falling within the scope of the general formula I and having a pharmaceutical activity are known (see for example D1-D6 or D10-D12).
 - 2.3 The subject-matter of claim 17 is not considered to fulfill the requirements of Art. 33(2) PCT with regard to D12 (see D12, claims 1, 4, 11, 13, 20 and 22



and page 3, lines 10-14 and 25-29).

- 2.4 Claims 36 and 38 refer to a method of preventing or treating obesity and the use of a compound of claim 1 for said treatment. However, compounds falling within the scope of the general formula I and their use in the treatment of obesity are known (see D1 and D11). Furthermore, D11 anticipates the subject-matter of claims 35 and 37. Therefore said claims do not comply with the requirements of Art. 33(2) PCT.

Inventive step

1. Without a clear limitation of the claims from the prior art, a meaningful examination of an inventive step (e.g. a proper problem solution approach) is not possible. However, the applicant is invited to take the following objections into consideration.
2. Even if the novelty of claim 1 could be established, for example by redrafting it as a proper second medical use claim, it would not be considered to meet the requirement of Art. 33(3) PCT for the following reasons:
It is common general knowledge that the properties of chemical compounds do largely depend on their chemical structure and that a person skilled in the art would expect that the properties of compounds would become the more similar the more similar their structure became. However, the structure of the compounds (I) in the present application may differ enormously, compare for example a compound with $\text{Ar}^1 = \text{cyclopentane}$, $\text{X} = \text{CH}_2$, $\text{Ar} = \text{benzene}$, $\text{Y} = \text{CH}_2$ and $\text{R}^1/\text{R}^2 = \text{hydrogen}$ with a compound with $\text{Ar}^1 = \text{phenyl substituted pyridine}$, $\text{X} = -\text{CH}_2\text{CH}_2\text{CON}-$, $\text{Ar} = \text{indenyl}$, $\text{Y} = -\text{CH}_2\text{CH}_2-$, $\text{R}^1 = \text{hydrogen}$ and $\text{R}^2 = -\text{CH}_2\text{-phenyl}$, let alone those compounds whereby the variables may have "further substituents". It is further common general knowledge that even small structural modifications may change the biological activity significantly. It is therefore not credible that basically all compounds of the present invention will exhibit the desired activity (melanin-concentrating hormone antagonists). With regard to the available pharmaceutical data (compounds with $\text{Ar} = \text{biphenyl}$, $\text{X} = \text{CON}$, $\text{Ar} = \text{tetralinyl}$, $\text{Y} = \text{CH}_2$ and $\text{R}^1/\text{R}^2 = \text{unsubstituted alkyl}$), claim 1 is regarded as unreasonable generalisation of the structures



shown in the examples.

3. The same objection is valid for the compounds of claims 18-31 insofar as they "may have substituents". Such an expression technically means substituted by absolutely everything. However, it is apparently rather doubtful that the use of every possible substituent may result in compounds having the desired activity and therefore solving the underlying technical problem of providing compounds having a melanin-concentrating antagonistic activity.

Industrial applicability

For the assessment of the present claims 35 and 36 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

VII. Certain defects

Claims 19, 22, 25, 28, 29, 30 and 31 all refer to compounds falling within the scope of the compounds as defined in claim 18. They comprise all the features of claim 18 and are therefore not appropriately formulated as a claim dependent on the latter (Rule 6.4 PCT).

VIII. Certain observations

1. Claims 1-38 are not supported by the description as required by Article 6 PCT, as their scope is broader than justified by the description and drawings. The reasons therefore are the following:
The term "having further substituents" includes compounds substituted by absolutely everything. Such an open claim is not considered to comply with the



requirement of Art. 6 PCT. Furthermore, the desired activity over the whole scope of the claims has not been demonstrated and is also considered to be doubtful (see also item V).

2. The proviso in claim 18 is not considered to be clear with regard to the compound within the brackets. It is not apparent if said compound is excluded from or included in the scope of claim 18.
3. Claim 32 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The following functional statements do not enable the skilled person to determine which technical features are necessary to perform the stated functions: "**prodrug** of a compound as defined...".
4. Some of the compounds mentioned in claim 34 are not included in the definition of the compounds according claim 18, for example page 347, lines 32-33, page 348, lines 2-3, 24-25, 34-35. This inconsistency between the claims leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT).
A similar inconsistency can be found between the examples 90, 91, 109, 110, 143, 213-4, 219, 220, 247, 248, 251 and claim 18.



PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 2648W00P	FOR FURTHER ACTION		see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/JP 00/ 06375	International filing date (day/month/year) 19/09/2000	(Earliest) Priority Date (day/month/year) 20/09/1999	
Applicant TAKEDA CHEMICAL INDUSTRIES, LTD.			

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ **None of the figures.**



INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 00/06375**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 35 and 36 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-33(partly), 35-38(partly)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.



FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-33(partly), 35-38(partly)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty (attention is drawn to the fact that claim 1 as it is drafted has to be considered purely as a compound claim). So many documents were retrieved (a few have been cited as a mere random selection) that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search has been restricted to:

compounds to formula I' (see claim 18) with $X = C(O)N$, $Y = -(CH_2)_2-$ whereby the substituents $Al-X-$ and YNR_1R_2 may not be attached in alpha-position to the C-atoms shared by the condensed ring (Ar'). Ar' , Ar and R_1/R_2 are as defined in claim 18.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.



INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 00/06375

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C235/42 C07C235/84 C07D209/48 C07C237/40 C07C275/42
 C07C233/44 A61K31/16 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, WPI Data, EPO-Internal, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 32967 A (SMITHKLINE BEECHAM PLC ;HAM PETER (GB); GASTER LARAMIE MARY (GB);) 7 December 1995 (1995-12-07) cited in the application claims; examples ---	1-5,7, 13-16
X	WO 98 38156 A (KATO KANEYOSHI ;TERAUCHI JUN (JP); FUKUMOTO HIROAKI (JP); KAKIHANA) 3 September 1998 (1998-09-03) claims; examples ---	1-7,9-16
X	WO 99 01127 A (BONDINELL WILLIAM E ;SMITHKLINE BEECHAM CORP (US); CHAN JAMES A (U) 14 January 1999 (1999-01-14) claim 4; examples --- -/--	1-7, 9-16,18, 29,32



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

° Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

19 December 2000

Date of mailing of the international search report

15. 01. 01

Name and mailing address of the ISA

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 Fax: (+31-70) 340-3016

Authorized officer

Seufert, G



INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 00/06375

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 21 08 185 A (TROPONWERKE DINKLAGE & CO.) 7 September 1972 (1972-09-07) claims; examples ---	1-4, 8-16, 18, 28, 32
X	DE 24 48 257 A (TROPONWERKE DINKLAGE & CO) 22 April 1976 (1976-04-22) claims; examples ---	1-4, 8-16
X	DE 25 02 588 A (TROPONWERKE DINKLAGE & CO) 29 July 1976 (1976-07-29) claims; examples ---	1-4, 8-16
X	R. E. MEWSHAW ET AL.: "New Generation Dopaminergic Agents. 1. Discovery of a Novel Scaffold Which Embraces the D2 Agonist Pharmacophore. Structure-Activity Relationship of a Series of 2-(Aminomethyl)chromans" J. MED. CHEM., vol. 40, no. 26, 1997, pages 4235-56, XP002155829 * page 4248, right column, example 22b - page 4249, left column, example 39a * ---	1-4, 7, 9, 11-13
X	A. M. BIRCH ET AL.: "N-Substituted (2,3-Dihydro-1,4-benzodioxin-2-yl)methylam ine Derivatives as D2 Antagonists/5-HT1A Partial Agonists with Potential as Atypical Antipsychotic Agents" J. MED. CHEM., vol. 42, no. 17, 1999, pages 3342-55, XP002155830 * scheme 8 compound 49 * ---	1-4, 7, 9, 11-13
X	DATABASE BEILSTEIN 'Online! Beilstein Informationssysteme; XP002155831 * see BRN 5345411 * & J. CHEM. SOC. PERKIN TRANS. 1, vol. 5, 1992, pages 531-32, ---	1-4, 7, 9, 11-13
X	EP 0 533 266 A (GLAXO GROUP LTD) 24 March 1993 (1993-03-24) cited in the application claims; examples ---	1, 4, 5, 7, 9, 10, 13-16
X	WO 96 35671 A (DOW ROBERT L ; PFIZER (US)) 14 November 1996 (1996-11-14) cited in the application claims; examples ---	1, 4, 7, 13-16, 36, 38

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 00/06375

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 920 864 A (PFIZER PROD INC) 9 June 1999 (1999-06-09) * page 3, line 10-14, 30-36; claims; examples *	1,4,7, 13-17, 35-38
A	QU D ET AL: "A ROLE FOR MELANIN-CONCENTRATING HORMONE IN THE CENTRAL REGULATION OF FEEDING BEHAVIOUR" NATURE,GB,MACMILLAN JOURNALS LTD. LONDON, vol. 380, 21 March 1996 (1996-03-21), pages 243-247, XP002037981 ISSN: 0028-0836 the whole document	1-38



INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 00/06375

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9532967	A	07-12-1995	AU 2565595	A	21-12-1995
			EP 0763034	A	19-03-1997
			JP 10500960	T	27-01-1998
			US 5756496	A	26-05-1998
			ZA 9504330	A	17-05-1996
WO 9838156	A	03-09-1998	AU 6116698	A	18-09-1998
			EP 0971878	A	19-01-2000
			JP 11080098	A	23-03-1999
WO 9901127	A	14-01-1999	AU 8381398	A	25-01-1999
			BR 9810758	A	15-08-2000
			CN 1261795	T	02-08-2000
			EP 1001766	A	24-05-2000
			NO 996490	A	27-12-1999
			ZA 9805542	A	07-04-1999
DE 2108185	A	07-09-1972	AT 312593	B	15-12-1973
			AT 308090	B	15-05-1973
			AU 459412	B	27-03-1975
			AU 3108771	A	18-01-1973
			BE 769959	A	13-01-1972
			CA 960669	A	07-01-1975
			CH 563385	A	30-06-1975
			CH 563386	A	30-06-1975
			CH 564006	A	15-07-1975
			CH 563384	A	30-06-1975
			CS 172355	B	29-12-1976
			DK 125919	B	21-05-1973
			ES 393295	A	01-03-1975
			FI 54117	B	30-06-1978
			FR 2100927	A	24-03-1972
			GB 1323179	A	11-07-1973
			IL 37284	A	22-10-1974
			NL 7109845	A	19-01-1972
			OA 3762	A	24-12-1971
			RO 59060	A	15-01-1976
			SE 379541	B	13-10-1975
			SU 402211	A	12-10-1973
			SU 404237	A	26-10-1973
			SU 461494	A	25-02-1975
			SU 433678	A	25-06-1974
			US 3897426	A	29-07-1975
			US 3930003	A	30-12-1975
			YU 184271	A, B	10-07-1979
DE 2448257	A	22-04-1976	NONE		
DE 2502588	A	29-07-1976	NONE		
EP 0533266	A	24-03-1993	AU 2452992	A	25-03-1993
			CA 2078506	A	19-03-1993
			CN 1071922	A	12-05-1993
			CZ 9202855	A	14-04-1993
			FI 924159	A	19-03-1993
			HU 66319	A	28-11-1994
			JP 6107649	A	19-04-1994
			MX 9205279	A	01-03-1993



INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 00/06375

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0533266	A		NO 923617 A	19-03-1993
			PL 295961 A	06-09-1993
			US 5356893 A	18-10-1994
			ZA 9207107 A	08-09-1993
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WO 9635671	A	14-11-1996	CA 2220399 A	14-11-1996
			HU 9601240 A	29-09-1997
			AU 4747599 A	02-12-1999
			AU 706235 B	10-06-1999
			AU 5218596 A	21-11-1996
			BR 9602209 A	07-04-1998
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			EP 0824519 A	25-02-1998
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<hr/>				
EP 0920864	A	09-06-1999	AU 9605598 A	24-06-1999
			HU 9802795 A	30-08-1999
			JP 11228447 A	24-08-1999
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 2648WO0P	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/JP00/06375	International filing date (day/month/year) 19/09/2000	Priority date (day/month/year) 20/09/1999
International Patent Classification (IPC) or national classification and IPC C07C235/00		
Applicant TAKEDA CHEMICAL INDUSTRIES, LTD. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 9 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 11/04/2001	Date of completion of this report 20.12.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Seufert, G Telephone No. +49 89 2399 8330 

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-335 as originally filed

Claims, No.:

1-38 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 1-33 (partly), 35-38(partly) .

because:

- ☒ the said international application, or the said claims Nos. 35, 36 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the said claims Nos. 1-33 (partly), 35-38 (partly).
2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:
- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims 19-27, 30, 31
	No: Claims 1-18, 28, 29, 32, 35-38
Inventive step (IS)	Yes: Claims
	No: Claims 1-38
Industrial applicability (IA)	Yes: Claims 1-34, 37, 38

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/JP00/06375

No: Claims 35, 36

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet



Reference is made to the following documents:

- D1 WO-A-9901127
- D2 DE-A-2108185
- D3 WO-A-9532967
- D4 WO-A-9838156
- D5 DE-A-2448257
- D6 DE-A-2502588
- D7 J. Med. Chem. 40(26), 1997, 4235-56
- D8 J. Med. Chem. 42(17), 1999, 3342-55
- D9 Beilstein Database, BRN 5345411 & J. Chem. Soc. Perkin Trans 1, 5, 1992, 531-2
- D10 EP-A-533266
- D11 WO-A-9635671
- D12 EP-A-920864
- D13 Nature, 380, 1996, 243-47

III. Non establishment of opinion

According to Rule 66.1e the International Preliminary Examination Authority is not required to carry out an examination on subject-matter for which no search report as been established.

The applicant has been informed by the Search Authority that a meaningful search has not been possible considering the large amount of documents relevant to the issue of novelty. The search has been restricted to the group of compounds as defined on the supplementary sheet included in the search report.

Consequently, a complete examination with regard to novelty, inventive step and industrial applicability has only been carried out for that group of compounds.

Claims 35 and 36 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).



V. Reasoned statement under Art. 35(2) PCT with regard to novelty, inventive step and industrial applicability

Novelty

1. Claim 18 refers to compounds of the general formula (I) and claim 28 and 29 to subgroups of said general formula. Documents D1 and D2 anticipate compounds falling within the scope of claims 18, 28 and 29 (see D1, claim 4 and D2, claims and examples) and their pharmaceutical use. Therefore, claims 18, 28 and 29 as well as claim 32 are not considered to meet the requirement of Art. 33(2) PCT.
2. As mentioned above, the search has been restricted to a certain group of compounds according to claim 18 and only for those, the examination may be considered complete. However, with regard to the documents mentioned in the search report some preliminary remarks with regard to novelty of the rest of the subject-matter can be made.
 - 2.1 Although the subject-matter of claim 1 has not been searched completely, it is obvious that compounds of the general formula I are by no means new, (see documents D1-D12). Claim 1 is thereby considered as a claim referring to a compound of the formula (I). The expression "a melanin-concentrating hormone antagonist" is not considered to be limiting. Thus, claim 1 and the dependent claims 2-13 are not considered to meet the requirement of Art. 33(2) PCT.
 - 2.2 Similarly claims 14-16 are not considered to meet the requirements of Art. 33(2) PCT. A first medical use claim (i.e. "a compound for treating...") is only considered to be novel if the compounds are not known for any pharmaceutical activity. However, compounds falling within the scope of the general formula I and having a pharmaceutical activity are known (see for example D1-D6 or D10-D12).
 - 2.3 The subject-matter of claim 17 is not considered to fulfill the requirements of Art. 33(2) PCT with regard to D12 (see D12, claims 1, 4, 11, 13, 20 and 22

and page 3, lines 10-14 and 25-29).

- 2.4 Claims 36 and 38 refer to a method of preventing or treating obesity and the use of a compound of claim 1 for said treatment. However, compounds falling within the scope of the general formula I and their use in the treatment of obesity are known (see D1 and D11). Furthermore, D11 anticipates the subject-matter of claims 35 and 37. Therefore said claims do not comply with the requirements of Art. 33(2) PCT.

Inventive step

1. Without a clear limitation of the claims from the prior art, a meaningful examination of an inventive step (e.g. a proper problem solution approach) is not possible. However, some preliminary remarks can already be made.
2. Even if the novelty of claim 1 could be established, for example by redrafting it as a proper second medical use claim, it would not be considered to meet the requirement of Art. 33(3) PCT for the following reasons:
It is common general knowledge that the properties of chemical compounds do largely depend on their chemical structure and that a person skilled in the art would expect that the properties of compounds would become the more similar the more similar their structure became. However, the structure of the compounds (I) in the present application may differ enormously, compare for example a compound with $Ar^1 = \text{cyclopentane}$, $X = CH_2$, $Ar = \text{benzene}$, $Y = CH_2$ and $R^1/R^2 = \text{hydrogen}$ with a compound with $Ar^1 = \text{phenyl substituted pyridine}$, $X = -CH_2CH_2CON-$, $Ar = \text{indenyl}$, $Y = -CH_2CH_2-$, $R^1 = \text{hydrogen}$ and $R^2 = -CH_2-$ phenyl, let alone those compounds whereby the variables may have "further substituents". It is further common general knowledge that even small structural modifications may change the biological activity significantly. It is therefore not credible that basically all compounds of the present invention will exhibit the desired activity (melanin-concentrating hormone antagonists). With regard to the available pharmaceutical data (compounds with $Ar = \text{biphenyl}$, $X = CON$, $Ar = \text{tetralinyl}$, $Y = CH_2$ and $R^1/R^2 = \text{unsubstituted alkyl}$), claim 1 is regarded as unreasonable generalisation of the structures shown in the examples.

3. The same objection is valid for the compounds of claims 18-31 insofar as they "may have substituents". Such an expression technically means substituted by absolutely everything. However, it is apparently rather doubtful that the use of every possible substituent may result in compounds having the desired activity and therefore solving the underlying technical problem of providing compounds having a melanin-concentrating antagonistic activity.

Industrial applicability

For the assessment of the present claims 35 and 36 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

VII. Certain defects

Claims 19, 22, 25, 28, 29, 30 and 31 all refer to compounds falling within the scope of the compounds as defined in claim 18. They comprise all the features of claim 18 and are therefore not appropriately formulated as a claim dependent on the latter (Rule 6.4 PCT).

VIII. Certain observations

1. Claims 1-38 are not supported by the description as required by Article 6 PCT, as their scope is broader than justified by the description and drawings. The reasons therefore are the following:
The term "having further substituents" includes compounds substituted by absolutely everything. Such an open claim is not considered to comply with the requirement of Art. 6 PCT. Furthermore, the desired activity over the whole scope of the claims has not been demonstrated and is also considered to be doubtful

(see also item V).

2. The proviso in claim 18 is not considered to be clear with regard to the compound within the brackets. It is not apparent if said compound is excluded from or included in the scope of claim 18.
3. Claim 33 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The following functional statements do not enable the skilled person to determine which technical features are necessary to perform the stated functions: "prodrug of a compound as defined...".
4. Some of the compounds mentioned in claim 34 are not included in the definition of the compounds according claim 18, for example page 347, lines 32-33, page 348, lines 2-3, 24-25, 34-35. This inconsistency between the claims leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT).
A similar inconsistency can be found between the examples 90, 91, 109, 110, 143, 213-4, 219, 220, 247, 248, 251 and claim 18.



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A61K 31/16, 31/40

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patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

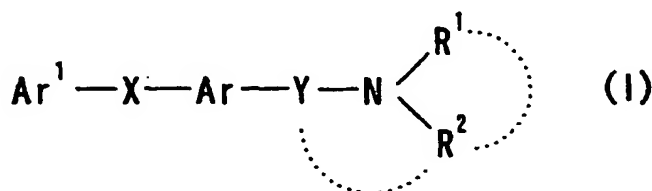
Published:

— with international search report

(88) Date of publication of the international search report:
4 October 2001

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: MELANIN CONCENTRATING HORMONE ANTAGONIST



which may have substituents; R¹ and R², together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; R² may form a spiro ring together with Ar; or R², together with the adjacent nitrogen atom and Y, may form a nitrogen-containing hetero ring which may have substituents; or a salt thereof; which is useful as an agent for preventing or treating obesity, etc.

(57) Abstract: A melanin-concentrating hormone antagonist which comprises a compound of formula (I) wherein Ar¹ is a cyclic group which may have substituents; X is a spacer having a main chain of 1 to 6 atoms; Y is a bond or a spacer having a main chain of 1 to 6 atoms; Ar is a monocyclic aromatic ring which may be condensed with a 4 to 8 membered non-aromatic ring, and may have further substituents; R¹ and R² are independently hydrogen atom or a hydrocarbon group

INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 00/06375

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C235/42 C07C233/44 A61K31/16 C07D209/48 A61K31/40 C07C237/40 C07C275/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, WPI Data, EP0-Internal, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 32967 A (SMITHKLINE BEECHAM PLC ;HAM PETER (GB); GASTER LARAMIE MARY (GB);) 7 December 1995 (1995-12-07) cited in the application claims; examples	1-5,7, 13-16
X	WO 98 38156 A (KATO KANEYOSHI ;TERAUCHI JUN (JP); FUKUMOTO HIROAKI (JP); KAKIHANA) 3 September 1998 (1998-09-03) claims; examples	1-7,9-16
X	WO 99 01127 A (BONDINELL WILLIAM E ;SMITHKLINE BEECHAM CORP (US); CHAN JAMES A (U) 14 January 1999 (1999-01-14) claim 4; examples	1-7, 9-16,18, 29,32
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

19 December 2000

Date of mailing of the international search report

15. 01. 01

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Authorized officer

Seufert, G

INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 00/06375

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 21 08 185 A (TROPONWERKE DINKLAGE & CO.) 7 September 1972 (1972-09-07) claims; examples ---	1-4, 8-16, 18, 28, 32
X	DE 24 48 257 A (TROPONWERKE DINKLAGE & CO) 22 April 1976 (1976-04-22) claims; examples ---	1-4, 8-16
X	DE 25 02 588 A (TROPONWERKE DINKLAGE & CO) 29 July 1976 (1976-07-29) claims; examples ---	1-4, 8-16
X	R. E. MEWSHAW ET AL.: "New Generation Dopaminergic Agents. 1. Discovery of a Novel Scaffold Which Embraces the D2 Agonist Pharmacophore. Structure-Activity Relationship of a Series of 2-(Aminomethyl)chromans" J. MED. CHEM., vol. 40, no. 26, 1997, pages 4235-56, XP002155829 * page 4248, right column, example 22b - page 4249, left column, example 39a * ---	1-4, 7, 9, 11-13
X	A. M. BIRCH ET AL.: "N-Substituted (2,3-Dihydro-1,4-benzodioxin-2-yl)methylamine Derivatives as D2 Antagonists/5-HT1A Partial Agonists with Potential as Atypical Antipsychotic Agents" J. MED. CHEM., vol. 42, no. 17, 1999, pages 3342-55, XP002155830 * scheme 8 compound 49 * ---	1-4, 7, 9, 11-13
X	DATABASE BEILSTEIN 'Online! Beilstein Informationssysteme; XP002155831 * see BRN 5345411 * & J. CHEM. SOC. PERKIN TRANS. 1, vol. 5, 1992, pages 531-32, ---	1-4, 7, 9, 11-13
X	EP 0 533 266 A (GLAXO GROUP LTD) 24 March 1993 (1993-03-24) cited in the application claims; examples ---	1, 4, 5, 7, 9, 10, 13-16
X	WO 96 35671 A (DOW ROBERT L ; PFIZER (US)) 14 November 1996 (1996-11-14) cited in the application claims; examples ---	1, 4, 7, 13-16, 36, 38

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 00/06375

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 920 864 A (PFIZER PROD INC) 9 June 1999 (1999-06-09) * page 3, line 10-14, 30-36; claims; examples *	1, 4, 7, 13-17, 35-38
A	QU D ET AL: "A ROLE FOR MELANIN-CONCENTRATING HORMONE IN THE CENTRAL REGULATION OF FEEDING BEHAVIOUR" NATURE, GB, MACMILLAN JOURNALS LTD. LONDON, vol. 380, 21 March 1996 (1996-03-21), pages 243-247, XP002037981 ISSN: 0028-0836 the whole document	1-38



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INTERNATIONAL SEARCH REPORT

national application No.
PCT/JP 00/06375

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 35 and 36 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-33(partly), 35-38(partly)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.



FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

Continuation of Box I.2

Claims Nos.: 1-33(partly), 35-38(partly)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty (attention is drawn to the fact that claim 1 as it is drafted has to be considered purely as a compound claim). So many documents were retrieved (a few have been cited as a mere random selection) that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search has been restricted to:

compounds to formula I' (see claim 18) with $X = C(O)N$, $Y = -(CH_2)_2-$ whereby the substituents $Al-X-$ and $YNR1R2$ may not be attached in alpha-position to the C-atoms shared by the condensed ring (Ar'). Ar' , Ar and $R1/R2$ are as defined in claim 18.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.



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INTERNATIONAL SEARCH REPORT

Intr Application No
PCT/JP 00/06375

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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DE 2108185	A	07-09-1972	AT 312593 B AT 308090 B AU 459412 B AU 3108771 A BE 769959 A CA 960669 A CH 563385 A CH 563386 A CH 564006 A CH 563384 A CS 172355 B DK 125919 B ES 393295 A FI 54117 B FR 2100927 A GB 1323179 A IL 37284 A NL 7109845 A OA 3762 A RO 59060 A SE 379541 B SU 402211 A SU 404237 A SU 461494 A SU 433678 A US 3897426 A US 3930003 A YU 184271 A,B	15-12-1973 15-05-1973 27-03-1975 18-01-1973 13-01-1972 07-01-1975 30-06-1975 30-06-1975 15-07-1975 30-06-1975 29-12-1976 21-05-1973 01-03-1975 30-06-1978 24-03-1972 11-07-1973 22-10-1974 19-01-1972 24-12-1971 15-01-1976 13-10-1975 12-10-1973 26-10-1973 25-02-1975 25-06-1974 29-07-1975 30-12-1975 10-07-1979
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INTERNATIONAL SEARCH REPORT

Inter national Application No

PCT/JP 00/06375

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0533266 A		NO 923617 A PL 295961 A US 5356893 A ZA 9207107 A	19-03-1993 06-09-1993 18-10-1994 08-09-1993
WO 9635671 A	14-11-1996	CA 2220399 A HU 9601240 A AU 4747599 A AU 706235 B AU 5218596 A BR 9602209 A CZ 9601321 A EP 0824519 A FI 974172 A JP 11504649 T KR 190259 B NO 961887 A NZ 286548 A PL 314120 A SG 43365 A TR 960980 A US 5977124 A	14-11-1996 29-09-1997 02-12-1999 10-06-1999 21-11-1996 07-04-1998 12-03-1997 25-02-1998 07-11-1997 27-04-1999 01-06-1999 11-11-1996 25-03-1998 12-11-1996 17-10-1997 21-11-1996 02-11-1999
EP 0920864 A	09-06-1999	AU 9605598 A HU 9802795 A JP 11228447 A	24-06-1999 30-08-1999 24-08-1999



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DESCRIPTION

Melanin Concentrating Hormone Antagonist

5 TECHNICAL FIELD

The present invention relates to a melanin-concentrating hormone antagonist which is useful as an agent for preventing or treating obesity, etc.

10 BACKGROUND ART

Feeding behavior is an essential action for many living beings including humans. Therefore, if irregularities in feeding behavior occur, disorders, often connected to diseases, will occur in normal life-maintaining activities. Accompanying recent changes of our dietary environment, obesity is now becoming a social problem. In addition, not only is obesity a serious risk factor for life-style diseases such as diabetes, hypertension, and arteriosclerosis; it is also widely known that increased body weight places excessive burdens on joints such as knee joints, causing arthritis and pain.

The "diet boom," etc. show that there is a potentially great percentage of the population hoping to reduce body weight; on the other hand, many cases of feeding problems such as overeating, occurring due to causes such as hereditary neurosis or neurosis due to stress, have been reported.

Therefore, research on and development of agents for preventing or treating obesity, or agents for inhibiting eating, have been vigorously done for a long time.

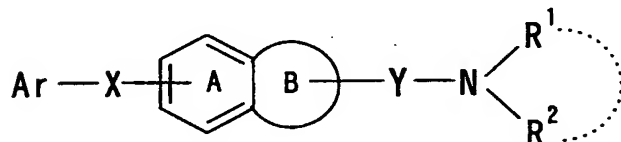
The centrally acting anorectic drug, Mazindol, is now being marketed.

Many appetite control factors such as leptin, have recently been discovered, and the development of anti-obesity agents or anorectic agents which will regulate the functions of these appetite control factors is progressing.

In particular, it is known that melanin- concentrating hormone (hereinafter also abbreviated as "MCH") originates in the hypothalamus and has orexigenic action. In addition, it has been reported that even though the daily behavior of MCH knock-out mice was normal, the amount of feeding by MCH knock-out mice was significantly reduced and their body weights were lighter than those of normal mice [Nature, Vol. 396, p.670, 1998]. This indicates that, if a MCH antagonist was produced, it can be expected to be an excellent anorectic agent or anti-obesity agent; but at present there are no known compound, especially non-peptide type compounds, which possess MCH antagonistic actions.

On the other hand, the following compounds are known as amine derivatives.

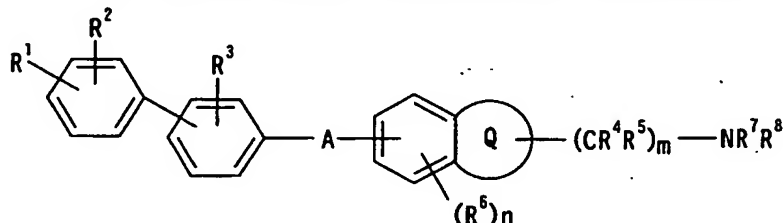
1) W098/38156 describes a compound of the formula :



wherein Ar is an optionally substituted ring assembly aromatic group or an optionally substituted condensed aromatic group; X is a bond, etc.; Y is an optionally substituted bivalent C₁₋₆ aliphatic hydrocarbon group which may have an intervening oxygen atom or sulfur atom; R¹ and R² are independently hydrogen atom or a lower alkyl, or R¹ and R², together with the adjacent nitrogen atom, form an optionally substituted nitrogen-containing hetero ring; Ring A is a benzene ring which may have further substituents in addition to the groups of the formula : -X-Ar where each symbol has the same meaning as defined above; Ring B is a 4 to 8 membered ring which may have further substituents in addition to the group of the formula : -Y-NR¹R² where each symbol has the same meaning as defined above; with the proviso that the condensed ring formed by ring A and ring B is an indole ring, the group of the formula : -X-Ar where

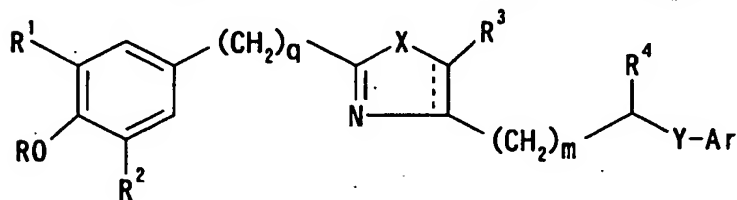
each symbol has the same meaning as defined above is substituted at the 4-, 6-, or 7- position on the indole ring; or its salt, which has an action of inhibiting the production and secretion of β -amyloid protein.

5 2) W095/32967 describes compound of the formula :



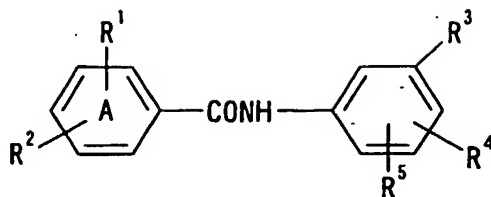
wherein A is CONR, in which R is hydrogen or C₁₋₆ alkyl; Q is an optionally substituted 5 to 7 membered hetero ring containing 1 to 3 hetero atoms selected from nitrogen or sulfur; R¹ is hydrogen, halogen, etc.; R² and R³ are independently hydrogen, halogen, etc.; R₄ and R₅ are independently hydrogen or C₁₋₆ alkyl; R⁶ is halogen, hydroxy, etc.; R₇ and R₈ are independently hydrogen, C₁₋₆ alkyls, etc.; m is 0 to 4; n is 0, 1 or 2; or its salt, which has 5HT_{1D} antagonist activity and can be expected to ameliorate anorexia.

3) W098/15274 describes a compound of the formula :

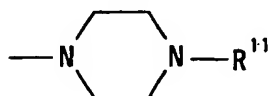


wherein Ar is phenyl, etc.; X is -O- or -S-; Y is CR⁵R^{5'} where R^{5'} is H and R⁵ is -H, etc.; Z is -CH₂- or -N-; R is H or -(C₁-C₆) alkyl; R¹ and R² are independently -(C₁-C₆) alkyl, etc.; R³ is H etc.; R⁴ is hydrogen, etc.; m is an integer of 0 to 2; q is 0 or 1; n is an integer of 0 to 4; p is an integer of 1 to 6; t is an integer of 1 to 4; which has an anti-oxidant activity and can be expected to ameliorate Alzheimer's disease.

4) EP533266



wherein R¹ is halogen, etc.; R² is phenyl optionally substituted by 1 or 2 substituents selected from halogen, etc.; R³ is

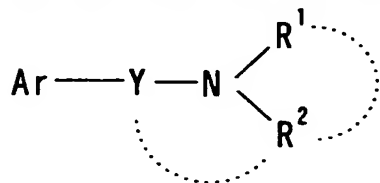


; R⁴ and R⁵ are independently hydrogen, halogen, etc.; R¹¹ is hydrogen or C₁₋₆ alkyl; which has 5HT_{1D} antagonist activity, and can be expected to ameliorate anorexia.

There has been great desire for the development of a melanin-concentrating hormone antagonist which is useful as an agent for preventing or treating obesity, excellent in oral absorbency, and safe.

DISCLOSURE OF INVENTION

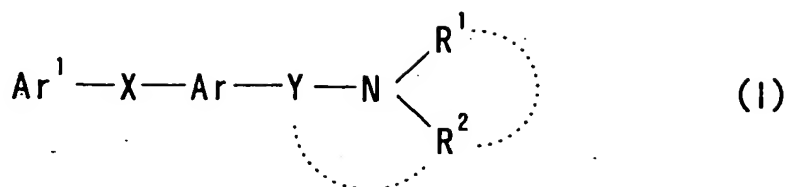
As a result of intensive studies of compounds with a MCH antagonistic action, the present inventors found that a derivative which is obtained by introducing a group of the formula : Ar¹-X- where each symbol has the same meaning as defined hereafter, into a compound of the formula :



wherein each symbol has the same meaning as defined hereinafter, had an excellent MCH antagonistic actions, to complete this invention.

Namely, the present invention relates to :

(1) a melanin-concentrating hormone antagonist which comprises a compound of the formula :



- wherein Ar¹ is a cyclic group which may have substituents;
 X is a spacer having a main chain of 1 to 6 atoms;
 Y is a bond or a spacer having a main chain of 1 to 6 atoms;
 5 Ar is a monocyclic aromatic ring which may be condensed with a 4 to 8 membered non-aromatic ring, and may have further substituents;
 R¹ and R² are independently hydrogen atom or a hydrocarbon group which may have substituents; R¹ and R², together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; R² may form a spiro ring together with Ar; or R², together with the adjacent nitrogen atom and Y, may form a nitrogen-containing hetero ring which may have substituents; or a salt thereof;
 10 (2) an antagonist according to the above (1), wherein Y is a spacer having a main chain of 1 to 6 atoms; R¹ and R² are independently hydrogen atom or a hydrocarbon group which may have substituents; R¹ and R², together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; or R² may form a spiro ring together with Ar;
 15 (3) an antagonist according to the above (2), wherein Ar¹ is an aromatic group which may have substituents; and "a hydrocarbon group which may have substituents" for R¹ and R² is "C₁₋₆ alkyl which may have substituents";
 20 (4) an antagonist according to the above (1), wherein the cyclic group for Ar¹ is C₆₋₁₄ monocyclic or condensed polycyclic aromatic hydrocarbon group;
 (5) an antagonist according to the above (1), wherein the
 30 cyclic group for Ar¹ is a group formed by removing an optional one hydrogen atom from an aromatic ring assemble in which 2 or 3 C₆₋₁₄ monocyclic or condensed polycyclic aromatic hydrocarbon groups are directly bonded by single

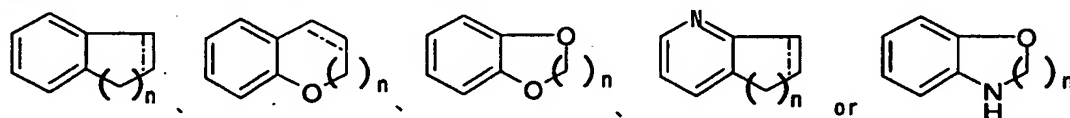
bonds;

(6) an antagonist according to the above (1), wherein the cyclic group for Ar¹ is a group formed by removing an optional one hydrogen atom from an aromatic ring assemble
5 in which C₆₋₁₄ monocyclic or condensed polycyclic aromatic hydrocarbon and 5 to 10 membered aromatic hetero ring are directly bonded by a single bond;

(7) an antagonist according to the above (1), wherein Ar¹ is phenyl, biphenyl, phenyl-pyridyl, phenyl-furyl,
10 phenyl-isoxazolyl, diphenyl-oxazolyl, pyridyl-phenyl, phenyl-pyrimidinyl, benzofuranyl-phenyl, furyl-phenyl, terphenyl, thienyl-phenyl, indolyl, naphthyl-oxadiazolyl, benzofuranyl-oxadiazolyl, benzothienyl, benzofuranyl, fluorenyl, pyridyl-pyrrolyl or
15 thioxanthanyl;

each of which may have 1 to 3 substituents selected from the group consisting of halogen atom; nitro; C₁₋₃ alkylenedioxy; optionally halogenated C₁₋₆ alkyl; hydroxy-C₁₋₆ alkyl; optionally halogenated C₃₋₆ cycloalkyl;
20 optionally halogenated C₁₋₆ alkoxy; optionally halogenated C₁₋₆ alkythio; hydroxy; C₇₋₁₉ aralkyloxy which may have substituents; C₆₋₁₄ aryloxy which may have substituents; amino; mono-C₁₋₆ alkylamino; di-C₁₋₆ alkylamino; 5 to 7 membered saturated cyclic amino which may have substituents
25 and may be condensed with a benzene ring; 5 to 7 membered non-aromatic heterocyclic groups which may have substituents; formyl; carboxy; C₆₋₁₄ aryl-carbonyl which may have substituents; C₆₋₁₄ aryl-carbamoyl which may have substituents; aromatic hetero ring-carbamoyl which may
30 have substituents; C₁₋₆ alkoxy-carbonyl; optionally halogenated C₁₋₆ alkyl-carboxamide; C₆₋₁₄ aryl-carboxamide which may have substituents; C₇₋₁₉ aralkyl-carboxamide which may have substituents; aromatic hetero ring-carboxamide which may have substituents; N-(C₆₋₁₄ aryl-carbonyl which
35 may have substituents)-N-C₁₋₆ alkylamino; C₆₋₁₄ arylamino-carbonylamino which may have substituents; C₆₋₁₄

- arylsulfonylamino which may have substituents; C₆₋₁₄
 aryl-carbonyloxy which may have substituents; oxo;
 carboxy-C₁₋₆ alkyl; C₁₋₆ alkoxy-carbonyl-C₁₋₆ alkyl; C₇₋₁₉
 aralkyl which may have substituents; aromatic hetero
 5 ring-C₁₋₆ alkoxy; and cyano;
- (8) an antagonist according to the above (1), wherein Ar¹
 is piperidinyl, piperazinyl, pyrrolidinyl, dihydropyridyl
 or tetrahydropyridyl; each of which may have 1 or 2
 substituents selected from the group consisting of oxo, C₆₋₁₄
 10 aryl which may have substituents, hydroxy, C₇₋₁₉
 aralkyloxy-carbonyl, and C₇₋₁₉ aralkyl;
- (9) an antagonist according to the above (1), wherein the
 "spacer having a main chain of 1 to 6 atoms" for X and Y
 is a bivalent group consisting of 1 to 3 species selected
 15 from -O-, -S-, -CO-, -SO-, -SO₂-, -NR⁸- (R⁸ is hydrogen
 atom, optionally halogenated C₁₋₆ alkyl, optionally
 halogenated C₁₋₆ alkyl-carbonyl, optionally halogenated C₁₋₆
 alkylsulfonyl), and a bivalent C₁₋₆ non-cyclic hydrocarbon
 group which may have substituents;
- 20 (10) an antagonist according to the above (1), wherein X
 is -CONR^{8c}-, -NR^{8c}CO-, -CH=CH-CONR^{8c}- or -SO₂NR^{8c}-
 wherein R^{8c} is hydrogen atom or C₁₋₆ alkyl;
- (11) an antagonist according to the above (1), wherein Y
 is an optionally halogenated bivalent C₁₋₆ non-cyclic
 25 hydrocarbon group;
- (12) an antagonist according to the above (1), wherein Ar
 is a ring of the formula :



- wherein ----- is a single bond or double bond, n is an integer
 30 of 1 to 4;
- (13) an antagonist according to the above (1), wherein R¹
 and R² are hydrogen atom or C₁₋₆ alkyl which may have
 substituents; or R¹ and R², together with the adjacent
 nitrogen atom, form a 3 to 8 membered nitrogen-containing

hetero ring;

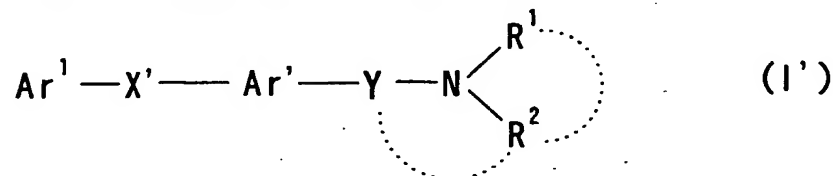
(14) an antagonist according to the above (1), which is an agent for preventing or treating diseases caused by a melanin-concentrating hormone;

5 (15) an antagonist according to the above (1), which is an agent for preventing or treating obesity;

(16) an antagonist according to the above (1), which is an anorectic agent;

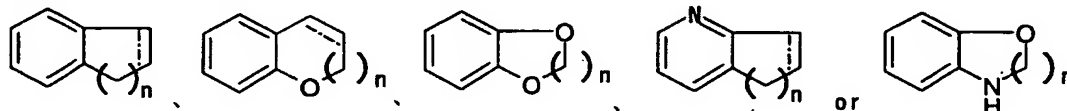
(17) a pharmaceutical, which comprises a melanin-concentrating hormone antagonist in combination with at least one species selected from the group consisting of an agent for treating diabetes, an agent for treating hypertension and an agent for treating arteriosclerosis;

(18) a compound of the formula :



15

wherein Ar^1 is a cyclic group which may have substituents;
 Ar' is a ring of the formula :



20 wherein ----- is a single bond or double bond, n is an integer of 1 to 4, and each ring may have substituents;

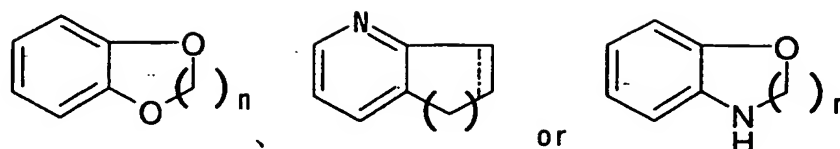
X' is $-\text{CONR}^{\text{sc}}-$, $-\text{NR}^{\text{sc}}\text{CO}-$, $-\text{CH}=\text{CH}-\text{CONR}^{\text{sc}}-$ or $-\text{SO}_2\text{NR}^{\text{sc}}-$ where R^{sc} is hydrogen atom or C_{1-6} alkyl;

Y is a spacer having a main chain of 1 to 6 atoms;

25 R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2 , together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; or R^2 , together with the adjacent nitrogen atom and Y , may form a nitrogen-containing hetero ring which may have substituents;

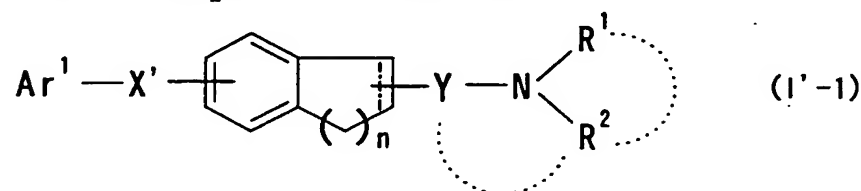
30

provided that Ar' is a ring of the formula :



wherein symbols have the same meanings as defined above,
and each ring may have substituents, when X' is -SO₂NH-;
and provided that Ar¹ is not biphenyl which may be
substituted, when X' is -CONH- and Ar' is any one of
benzopyran, dihydrobenzopyran, dihydrobenzoxazine,
dihydrobenzoxazole or tetrahydrobenzoxazepine;
(excluding N-[2-(N,N-dimethylamino)methyl-6-
tetralinyl]-4-biphenylcarboxamide); or a salt thereof;

(19) a compound of the formula :



wherein Ar¹ is a cyclic group which may have substituents;

----- is a single bond or double bond;

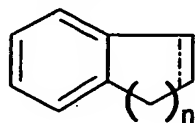
n is an integer of 1 to 4;

X' is -CONR^{8c}-, -NR^{8c}CO- or -CH=CH-CONR^{8c}- where R^{8c} is
hydrogen atom or C₁₋₆ alkyl;

Y is a spacer having a main chain of 1 to 6 atoms;

R¹ and R² are independently hydrogen atom or a hydrocarbon
group which may have substituents; R¹ and R², together with
the adjacent nitrogen atom, may form a nitrogen-containing
hetero ring which may have substituents; or R², together
with the adjacent nitrogen atom and Y, may form a
nitrogen-containing hetero ring which may have
substituents;

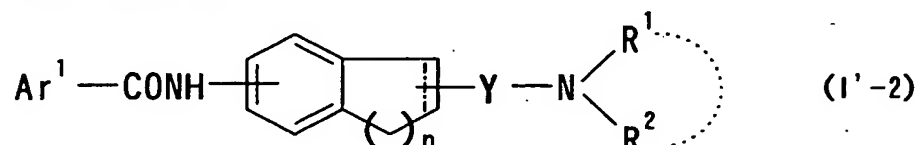
a ring of the formula :



wherein symbols have the same meanings as defined above,

may have further substituents;
provided that N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]-4-biphenylcarboxamide is excluded; or a salt thereof;

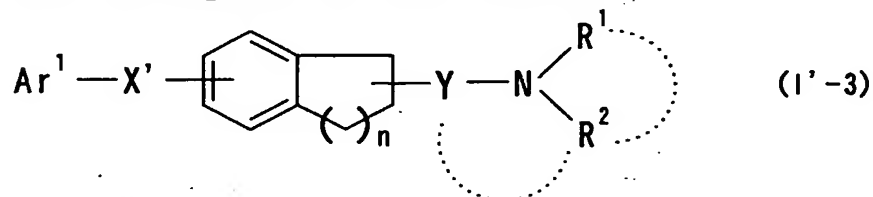
- 5 (20) a compound according to the above (19), which is of the formula :



- wherein R¹ and R² are independently hydrogen atom or a hydrocarbon group which may have substituents; R¹ and R², together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; the other symbols have the same meanings as defined in the above (19);

- (21) a compound according to the above (20), wherein Ar¹ is an aromatic group which may have substituents; and "a hydrocarbon group which may have substituents" for R¹ and R² is "C₁₋₆ alkyl which may have substituents";

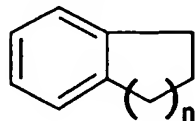
(22) a compound of the formula :



- wherein Ar¹ is a cyclic group which may have substituents;
n is an integer of 1 to 4;
X' is -CONR^{8c}-, -NR^{8c}CO- or -CH=CH-CONR^{8c}- where R^{8c} is hydrogen atom or C₁₋₆ alkyl;
Y is a spacer having a main chain of 1 to 6 atoms;
R¹ and R² are independently hydrogen atom or a hydrocarbon group which may have substituents; R¹ and R², together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; or R², together with the adjacent nitrogen atom and Y, may form a nitrogen-containing hetero ring which may have

substituents;

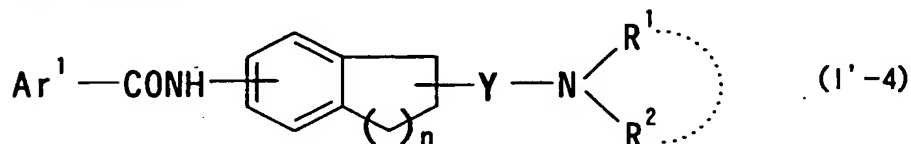
a ring of the formula :



wherein n has the same meaning as defined above, may have
5 further substituents;

provided that N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]-4-biphenylcarboxamide is excluded; or a salt thereof;

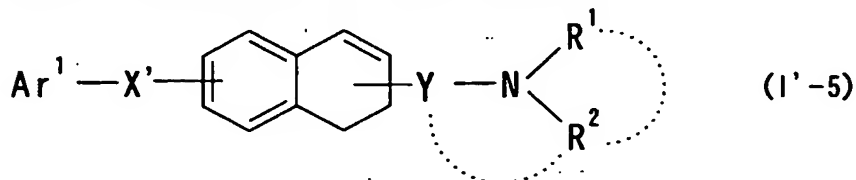
10 (23) a compound according to the above (22), which is of the formula :



wherein R¹ and R² are independently hydrogen atom or a hydrocarbon group which may have substituents; R¹ and R², together with the adjacent nitrogen atom, may form a
15 nitrogen-containing hetero ring which may have substituents; the other symbols have the same meanings as defined in the above (22);

(24) a compound according to the above (23), wherein Ar¹ is an aromatic group which may have substituents; and "a hydrocarbon group which may have substituents" for R¹ and R² is "C₁₋₆ alkyl which may have substituents";

(25) a compound of the formula :



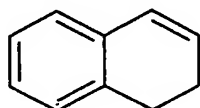
wherein Ar¹ is a cyclic group which may have substituents;
25 X' is -CONR^{8c}-, -NR^{8c}CO- or -CH=CH-CONR^{8c}- where R^{8c} is hydrogen atom or C₁₋₆ alkyl;

Y is a spacer having a main chain of 1 to 6 atoms;

R¹ and R² are independently hydrogen atom or a hydrocarbon

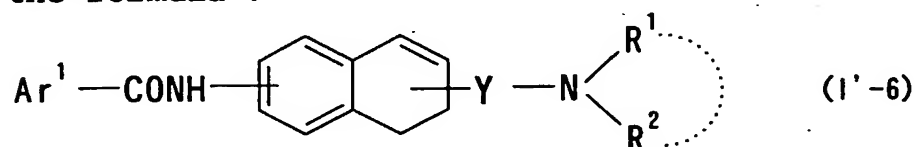
group which may have substituents; R^1 and R^2 , together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; or R^2 , together with the adjacent nitrogen atom and Y, may form a
 5 nitrogen-containing hetero ring which may have substituents;

a ring of the formula :



may have further substituents; or a salt thereof;

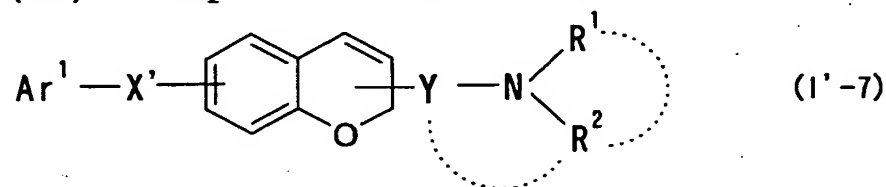
10 (26) a compound according to the above (25), which is of the formula :



wherein R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2 , together with the adjacent nitrogen atom, may form a
 15 nitrogen-containing hetero ring which may have substituents; the other symbols have the same meanings as defined in the above (25);

(27) a compound according to the above (26), wherein Ar^1 is an aromatic group which may have substituents; and "a hydrocarbon group which may have substituents" for R^1 and R^2 is " C_{1-6} alkyl which may have substituents";

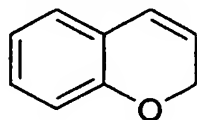
(28) a compound of the formula :



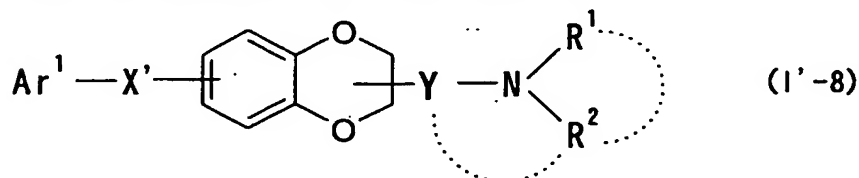
25 wherein Ar^1 is a cyclic group which may have substituents; X' is $-CONR^{8c}-$, $-NR^{8c}CO-$, $-CH=CH-CONR^{8c}-$ or $-SO_2NR^{8c}-$ where R^{8c} is hydrogen atom or C_{1-6} alkyl; Y is a spacer having a main chain of 1 to 6 atoms;

R¹ and R² are independently hydrogen atom or a hydrocarbon group which may have substituents; R¹ and R², together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; or R², together with the adjacent nitrogen atom and Y, may form a nitrogen-containing hetero ring which may have substituents;

a ring of the formula :

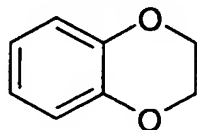


may have further substituents;
provided that Ar¹ is not biphenyl which may be substituted, when X' is -CONH-; or a salt thereof;
(29) a compound of the formula :

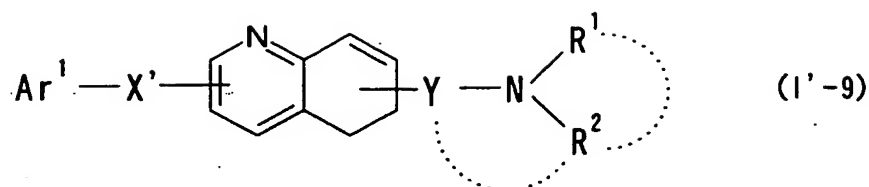


wherein Ar¹ is a cyclic group which may have substituents;
X' is -CONR^{8c}-, -NR^{8c}CO-, -CH=CH-CONR^{8c}- or -SO₂NR^{8c}- where R^{8c} is hydrogen atom or C₁₋₆ alkyl;
Y is a spacer having a main chain of 1 to 6 atoms;
R¹ and R² are independently hydrogen atom or a hydrocarbon group which may have substituents; R¹ and R², together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; or R², together with the adjacent nitrogen atom and Y, may form a nitrogen-containing hetero ring which may have substituents;

a ring of the formula :



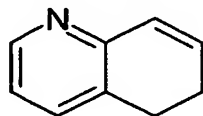
may have further substituents; or a salt thereof;
(30) a compound of the formula :



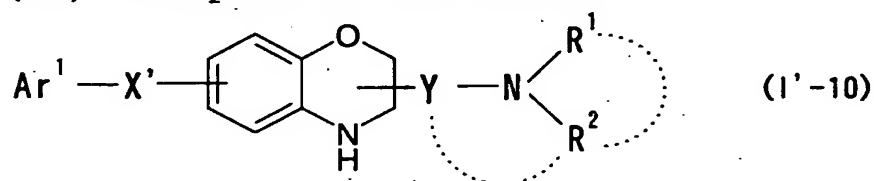
wherein Ar¹ is a cyclic group which may have substituents;
 X' is -CONR^{8c}-, -NR^{8c}CO-, -CH=CH-CONR^{8c}- or -SO₂NR^{8c}- where
 R^{8c} is hydrogen atom or C₁₋₆ alkyl;

- 5 Y is a spacer having a main chain of 1 to 6 atoms;
 R¹ and R² are independently hydrogen atom or a hydrocarbon
 group which may have substituents; R¹ and R², together with
 the adjacent nitrogen atom, may form a nitrogen-containing
 hetero ring which may have substituents; or R², together
 10 with the adjacent nitrogen atom and Y, may form a
 nitrogen-containing hetero ring which may have
 substituents;

a ring of the formula :



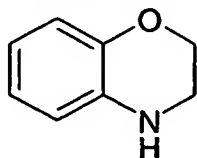
- 15 may have further substituents; or a salt thereof;
 (31) a compound of the formula :



wherein Ar¹ is a cyclic group which may have substituents;
 X' is -CONR^{8c}-, -NR^{8c}CO-, -CH=CH-CONR^{8c}- or -SO₂NR^{8c}- where
 20 R^{8c} is hydrogen atom or C₁₋₆ alkyl;

- Y is a spacer having a main chain of 1 to 6 atoms;
 R¹ and R² are independently hydrogen atom or a hydrocarbon
 group which may have substituents; R¹ and R², together with
 the adjacent nitrogen atom, may form a nitrogen-containing
 hetero ring which may have substituents; or R², together
 25 with the adjacent nitrogen atom and Y, may form a
 nitrogen-containing hetero ring which may have
 substituents;

a ring of the formula :



may have further substituents;

provided that Ar¹ is not biphenyl which may be

5 substituted, when X' is -CONH-; or a salt thereof;

(32) a pharmaceutical composition which comprises a compound as defined in any one of the above (18), (19), (22), (25), (26), (28), (29), (30) and (31);

(33) a prodrug of a compound as defined in any one of the above (18), (19), (22), (25), (26), (28), (29), (30) and (31);

(34) a compound according to the above (18), which is N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]-(4'-methoxybiphenyl-4-yl)carboxamide;

15 4'-fluoro-N-[6-[(N,N-dimethylamino)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide;

4'-fluoro-N-[6-(1-piperidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide;

20 4'-fluoro-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide;

(+)-4'-fluoro-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide;

25 (-)-4'-fluoro-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide;

4'-chloro-N-[3-[(N,N-dimethylamino)methyl]-2H-chromen-7-yl][1,1'-biphenyl]-4-carboxamide;

30 4'-fluoro-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide;

N-[3-[(dimethylamino)methyl]-2H-chromen-7-yl]-4'-fluoro[1,1'-biphenyl]-4-carboxamide;

- 4'-chloro-N-[6-[(dimethylamino)methyl]-5-methyl-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide;
6-(4-methoxyphenyl)-N-[5-methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]nicotinamide;
5 4'-chloro-N-[7-[(dimethylamino)methyl]-5,6-dihydro-3-quinolinyl][1,1'-biphenyl]-4-carboxamide;
4-(4-chlorophenyl)-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]-3,6-dihydro-1(2H)-
10 pyridinecarboxamide;
N-[6-[(dimethylamino)methyl]-7,8-dihydro-2-naphthalenyl]-4-(4-fluorophenyl)-1-piperidinecarboxamide;
4-(4-methoxyphenyl)-N-[6-(1-pyrrolidinylmethyl)-5-methyl-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide;
15 4'-fluoro-N-[6-[2-(1-pyrrolidinyl)ethyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide;
4'-chloro-N-[6-[2-(1-pyrrolidinyl)ethyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide;
20 4'-chloro-N-[2-[(dimethylamino)methyl]-3,4-dihydro-2H-1,4-benzoxazin-6-yl][1,1'-biphenyl]-4-carboxamide;
4-(4-methoxyphenyl)-N-[5-methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide;
25 4-(4-chlorophenyl)-N-[6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide;
4'-chloro-N-[2-[(dimethylamino)methyl]-1H-inden-6-yl][1,1'-biphenyl]-4-carboxamide;
30 4'-fluoro-N-[2-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-1,4-benzoxazin-6-yl][1,1'-biphenyl]-4-carboxamide;
4'-fluoro-N-[5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-
35 biphenyl]-4-carboxamide;
4'-chloro-N-[5-methyl-6-[(4-methyl-1-

piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide; or

4-(4-chlorophenyl)-N-[5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl]-1-

5 piperidinecarboxamide;

(35) a method for preventing or treating diseases caused by a melanin-concentrating hormone in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound or a salt thereof as defined in the above (1);

(36) a method for preventing or treating obesity in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound or a salt thereof as defined in the above (1);

15 (37) use of a compound or a salt thereof as defined in the above (1), for the manufacture of a pharmaceutical preparation for preventing or treating diseases caused by a melanin-concentrating hormone; and

(38) use of a compound or a salt thereof as defined in the above (1), for the manufacture of a pharmaceutical preparation for preventing or treating obesity.

Examples of "cyclic group" in the "cyclic group which may have substituents" for Ar¹ include aromatic groups, non-aromatic cyclic hydrocarbon groups, non-aromatic heterocyclic groups.

Here, examples of "aromatic groups" include monocyclic aromatic groups, condensed aromatic groups, and ring assembly aromatic groups.

30 Examples of the concerned monocyclic aromatic groups include univalent groups which can be formed by removing an optional one hydrogen atom from a monocyclic aromatic ring. Example of the "monocyclic aromatic ring" include a benzene ring and a 5 or 6 membered aromatic hetero ring.

35 Examples of the "5 or 6 membered aromatic hetero ring" include a 5 or 6 membered aromatic hetero ring containing

one or more (for example, 1 to 3) hetero atom selected from nitrogen, sulfur and oxygen atom in addition to a carbon atom. Concretely, thiophene, furan, pyrrole, imidazole, pyrazole, thiazole, isothiazole, oxazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, 1,2,4-oxadiazole, 1,3,4-oxadiazole, 1,2,4-thiadiazole, 1,3,4-thiadiazole, furazan, etc., can be mentioned.

Concrete examples of the "monocyclic aromatic groups" include phenyl, 2- or 3-thienyl, 2-, 3-, or 4-pyridyl, 2- or 3-furyl, 2-, 4- or 5-thiazonyl, 2-, 4- or 5-oxazolyl, 1-, 3- or 4-pyrazolyl, 2-pyrazinyl, 2-, 4- or 5-pyrimidinyl, 1-, 2- or 3-pyrrolyl, 1-, 2- or 4-imidazolyl, 3- or 4-pyridazinyl, 3-isothiazolyl, 3-isooxazolyl, 1,2,4-oxadiazol-5-yl, 1,2,4-oxadiazol-3-yl.

The "condensed aromatic groups" mean a univalent group that can be formed by removing an optional one hydrogen atom from condensed polycyclic (preferably bicyclic to tetracyclic, more preferably bicyclic or tricyclic) aromatic rings. Examples of the "condensed aromatic groups" include condensed polycyclic aromatic hydrocarbons, condensed polycyclic aromatic hetero rings.

Examples of the "condensed polycyclic aromatic hydrocarbons" include C₉₋₁₄ condensed polycyclic (bicyclic or tricyclic) aromatic hydrocarbons (e.g. naphthalene, indene, fluorene, anthracene, etc.).

Examples of the "condensed polycyclic aromatic hetero rings" include 9 to 14 membered, preferably, 9 or 10 membered, condensed polycyclic aromatic hetero rings containing one or more (for instance, 1 to 4 atoms) hetero atoms selected from nitrogen, sulfur and oxygen atom in addition to carbon atoms. Concrete examples of the "condensed polycyclic aromatic hetero rings" include benzofuran, benzimidazole, benzoxazole, benzothiazole, benzisothiazole, naphtho[2,3-b]thiophene, isoquinoline, quinoline, indole, quinoxaline, phenanthridine, phenothiadine, phenoxazine, phthaladine, naphthylidine,

quinazoline, cinnoline, carbazole, β -carboline, acridine, phenazine, phthalimide, thioxanthene.

Concrete examples of "condensed aromatic groups" include 1-naphthyl; 2-naphthyl; 2-, 3-, 4-, 5- or 8-quinolyl; 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl; 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl; 1-, 2-, 4- or 5-isoindolyl; 1-, 5- or 6-phthalazinyl; 2-, 3- or 5-quinoxalyl; 2-, 3-, 4-, 5- or 6-benzofuranyl; 2-, 4-, 5- or 6-benzothiazolyl; 1-, 2-, 4-, 5- or 6-benzimidazolyl; 1-, 2-, 3- or 4-fluorenyl; thioxanthenyl.

"Ring assembly aromatic group" means a group formed by removing an optional one hydrogen atom from an aromatic ring assemblies in which 2 or more (preferably 2 or 3) aromatic rings are directly bonded by single bonds, and in which the number of bonds which directly bond the rings, is less by one than the number of ring systems.

Examples of the aromatic ring assemblies include an aromatic ring assemblies formed by 2 or 3 (preferably 2) species selected from C_{6-14} monocyclic or condensed polycyclic aromatic hydrocarbons (e.g. benzene and naphthalene) and 5 to 10 membered (preferably 5 or 6 membered) aromatic hetero rings.

Preferable example of the aromatic ring assemblies include aromatic ring assemblies comprising 2 or 3 aromatic rings selected from benzene, naphthalene, pyridine, pyrimidine, thiophene, furan, thiazole, isothiazole, oxazole, isoxazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole, 1,2,4-thiadiazole, 1,3,4-thiadiazole, quinoline, isoquinoline, indole, benzothiophene, benzoxazole, benzothiazole, benzofuran and pyrrole.

Concrete examples of the "ring assembly aromatic groups" include 2-, 3- or 4-biphenyl; 3-(1-naphthyl)-1,2,4-oxadiazol-5-yl; 3-(2-naphthyl)-1, 2, 4-oxadiazol-5-yl; 3-(2-benzofuranyl)-1,2,4-oxadiazol-5-yl; 3-phenyl-1,2,4-oxadiazol-5-yl; 3-(2-benzoxazolyl)-1,2,4-oxadiazol-5-yl; 3-(3-indolyl)-1,2,4-oxadiazol-5-yl; 3-

(2-indolyl)-1,2,4-oxadiazol-5-yl; 4-phenylthiazol-2-yl;
4-(2-benzofuranyl)thiazol-2-yl; 4-phenyl-1,3-oxazol-5-
yl; 5-phenyl-isothiazol-4-yl; 5-phenyloxazol-2-yl; 4-
(2-thienyl)phenyl; 4-(3-thienyl)phenyl; 3-(3-
5 pyridyl)phenyl; 4-(3-pyridyl)phenyl; 6-phenyl-3-pyridyl;
5-phenyl-1,3,4-oxadiazol-2-yl; 4-(2-naphthyl)phenyl; 4-
(2-benzofuranyl)phenyl; 4,4'-terphenyl; 5-phenyl-2-
pyridyl; 2-phenyl-5-pyrimidinyl; 4-(4-pyridyl)phenyl;
2-phenyl-1,3-oxazol-5-yl; 2,4-diphenyl-1,3-oxazol-5-yl;
10 3-phenyl-isoxazol-5-yl; 5-phenyl-2-furyl; 4-(2-
furyl)phenyl; 3-(4-pyridyl)pyrrolyl.

Preferable groups among the above "aromatic groups"
are "C₆₋₁₄ monocyclic or condensed polycyclic aromatic
hydrocarbon groups (preferably, phenyl, etc.)", "a group
15 formed by removing an optional one hydrogen atom from an
aromatic ring assembles in which 2 or 3 C₆₋₁₄ monocyclic or
condensed polycyclic aromatic hydrocarbon groups are
directly bonded by single bonds (preferably, 2-, 3- or
4-biphenyl; 4,4'-terphenyl, etc.)" and "a group formed by
20 removing an optional one hydrogen atom from an aromatic ring
assembles in which a C₆₋₁₄ monocyclic or condensed polycyclic
aromatic hydrocarbon and 5 to 10 membered aromatic hetero
ring are directly bonded by a single bond (preferably,
6-phenyl-3-pyridyl, 5-phenyl-2-pyridyl, etc.)".

25 Examples of "non-aromatic cyclic hydrocarbon groups"
include C₃₋₈ Cycloalkyl, C₃₋₈ cycloalkenyl.

Here, concrete examples of C₃₋₈ cycloalkyl include
cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,
cycloheptyl, cyclooctyl.

30 Concrete examples of C₃₋₈ cycloalkenyl include
cyclopropenyl, cyclobutenyl, cyclopentenyl,
cyclohexenyl, cycloheptenyl, cyclooctenyl.

Among the above "non-aromatic cyclic hydrocarbon
groups", C₃₋₈ cycloalkyl is preferable, and cyclohexyl is
35 particularly preferable.

Examples of "non-aromatic heterocyclic groups"

include monocyclic non-aromatic heterocyclic groups,
condensed polycyclic non-aromatic heterocyclic groups.

Examples of the "monocyclic non-aromatic heterocyclic groups" include univalent groups formed by removing an optional one hydrogen atom from monocyclic non-aromatic hetero ring. Examples of the "monocyclic non-aromatic heterocyclic groups" include 5 to 8 membered monocyclic non-aromatic heterocyclic groups containing one or more (e.g. 1 to 3) hetero atoms selected from nitrogen, sulfur and oxygen atom in addition to carbon atoms. Concretely, tetrahydrothiophene, tetrahydrofuran, pyrrolidine, imidazoline, imidazolidine, pyrazoline, pyrazolidine, tetrahydrothiazole, tetrahydroisothiazole, tetrahydrooxazole, tetrahydroisoxazole, piperidine, tetrahydropyridine, dihydropyridine, piperazine, morpholine, thiomorpholine, tetrahydropyrimidine, tetrahydropyridazine, hexamethyleneimine, etc. can be mentioned.

"Condensed polycyclic non-aromatic heterocyclic group" means a univalent group formed by removing an optional one hydrogen atom from a condensed polycyclic (preferably bicyclic to tetracyclic, more preferably bicyclic or tricyclic) non-aromatic hetero ring. Examples of the "condensed polycyclic non-aromatic hetero ring" include 9 to 14 membered, preferably 9 or 10 membered condensed polycyclic non-aromatic hetero rings which contain one or more (e.g. 1 to 4) hetero atoms selected from nitrogen, sulfur and oxygen atom in addition to carbon atoms.

Concretely, dihydrobenzofuran, dihydrobenzimidazole, dihydrobenzoxazole, dihydrobenzothiazole, dihydrobenzisothiazole, dihydronaphtho[2,3-b]thiophene, tetrahydroisoquinoline, tetrahydroquinoline, indoline, isoindoline, tetrahydroquinoxaline, tetrahydrophenanthridine, hexahydrophenothiadine, hexahydrophenoxazine,

tetrahydrophthaladine, tetrahydronaphthylidine,
tetrahydroquinazoline, tetrahydrocinnoline,
tetrahydrocarbazole, tetrahydro- β -carboline,
tetrahydroacridine, tetrahydrophenazine,
5 tetrahydrothioxantene, etc., can be mentioned.

Among the above "non-aromatic heterocyclic groups",
"5 to 8 membered monocyclic non-aromatic heterocyclic
groups (preferably piperidinyl; piperazinyl;
pyrrolidinyl; dihydropyridyl; tetrahydropyridyl, etc.)"
10 are preferable.

Examples of "substituents" in the "cyclic group which
may have substituents" for Ar¹ include oxo, halogen atoms
(e.g. fluorine, chlorine, bromine, iodine, etc.), C₁₋₃
15 alkylenedioxy (e.g. methylenedioxy, ethylenedioxy, etc.),
nitro, cyano, optionally halogenated C₁₋₆ alkyl, hydroxy-C₁₋₆
alkyl, carboxy-C₁₋₆ alkyl, C₁₋₆ alkoxy-carbonyl-C₁₋₆ alkyl,
C₆₋₁₄ aryloxy-C₁₋₆ alkyl (e.g. phenoxymethyl, etc.), C₁₋₆
alkyl-C₆₋₁₄ aryl-C₂₋₆ alkenyl (e.g. methylphenylethenyl,
20 etc.), optionally halogenated C₃₋₆ cycloalkyl, optionally
halogenated C₁₋₆ alkoxy, optionally halogenated C₁₋₆
alkylthio, C₇₋₁₉ aralkyl which may have substituents,
hydroxy, C₆₋₁₄ aryloxy which may have substituents, C₇₋₁₉
aralkyloxy which may have substituents, C₆₋₁₄ aryl-carbamoyl
25 which may have substituents, amino, amino-C₁₋₆ alkyl (e.g.
aminomethyl, aminoethyl, aminopropyl, aminobutyl, etc.),
mono-C₁₋₆ alkylamino (e.g. methylamino, ethylamino,
propylamino, isopropylamino, butylamino, etc.), di-C₁₋₆
alkylamino (e.g. dimethylamino, diethylamino,
30 dipropylamino, dibutylamino, ethylmethylamino, etc.),
mono-C₁₋₆ alkylamino-C₁₋₆ alkyl (e.g. methylaminomethyl,
ethylaminomethyl, propylaminomethyl,
isopropylaminoethyl, butylaminoethyl, etc.), di-C₁₋₆
alkylamino-C₁₋₆ alkyl (e.g. dimethylaminomethyl,
35 diethylaminomethyl, dipropylaminomethyl,
diisopropylaminoethyl, dibutylaminoethyl, etc.), 5 to 7

membered saturated cyclic amino which may have substituents, 5 to 7 membered non-aromatic heterocyclic groups which may have substituents, acyl, acylamino, acyloxy, aromatic hetero ring-C₁₋₆ alkoxy.

5 The "cyclic group" for Ar¹ may have 1 to 5, preferably 1 to 3, of the above-mentioned substituents at a substitutable position on the cyclic group. When the number of substituents is 2 or more, each substituents can be the same or different.

10 Also, when the "cyclic group" for Ar¹ is a non-aromatic cyclic hydrocarbon group or a non-aromatic heterocyclic group, the "cyclic group" may have as its substituents, C₆₋₁₄ aryl which may have substituents, and 5 to 10 membered aromatic heterocyclic groups which may have substituents.

15 Here, the groups exemplified as "substituents" in the "5 to 7 membered saturated cyclic amino which may have substituents" mentioned hereinafter, can be mentioned as "C₆₋₁₄ aryl which may have substituents" and "5 to 10 membered aromatic heterocyclic groups which may have substituents".

20 The number of substituents is, for instance, 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

Concrete examples of the above "optionally halogenated C₁₋₆ alkyl" include C₁₋₆ alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.) which may have 1 to 5, preferably 1 to 3, halogen atoms (e.g. fluorine, chlorine, bromine, iodine, etc.). Concrete examples include methyl, chloromethyl, difluoromethyl, trichloromethyl, trifluoromethyl, ethyl, 2-bromoethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, propyl, 3,3,3-trifluoropropyl, isopropyl, butyl, 4,4,4-trifluorobutyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 5,5,5-trifluoropentyl, hexyl, 6,6,6-trifluorohexyl.

The C₁₋₆ alkyl in the above "optionally halogenated C₁₋₆

alkyl" can be mentioned as the C_{1-6} alkyl in the above "hydroxy- C_{1-6} alkyl", "carboxy- C_{1-6} alkyl" and " C_{1-6} alkoxy-carbonyl- C_{1-6} alkyl". Examples of C_{1-6} alkoxy in the " C_{1-6} alkoxy-carbonyl- C_{1-6} alkyl" include methoxy, ethoxy, propoxy, butoxy, pentyloxy.

Examples of the above "optionally halogenated C_{3-6} cycloalkyl" include C_{3-6} cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.) which may have 1 to 5, preferably 1 to 3, halogen atoms (e.g. fluorine, chlorine, bromine, iodine, etc.). Concrete examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4,4-dichlorocyclohexyl, 2,2,3,3-tetrafluorocyclopentyl, 4-chlorocyclohexyl.

Examples of the above "optionally halogenated C_{1-6} alkoxy" include C_{1-6} alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy, pentyloxy, etc.) which may have 1 to 5, preferably 1 to 3, halogen atoms (e.g. fluorine, chlorine, bromine, iodine, etc.). Concrete examples include methoxy, difluoromethoxy, trifluoromethoxy, ethoxy, 2,2,2-trifluoroethoxy, propoxy, isopropoxy, butoxy, 4,4,4-trifluorobutoxy, isobutoxy, sec-butoxy, pentyloxy, hexyloxy.

Examples of the above "optionally halogenated C_{1-6} alkylthio" include C_{1-6} alkylthio (e.g. methylthio, ethylthio, propylthio, isopropylthio, butylthio, sec-butylthio, tert-butylthio, etc.) which may have 1 to 5, preferably 1 to 3, halogen atoms (e.g. fluorine, chlorine, bromine, iodine, etc.). Concrete examples include methylthio, difluoromethylthio, trifluoromethylthio, ethylthio, propylthio, isopropylthio, butylthio, 4,4,4-trifluorobutylthio, pentylthio, hexylthio.

Examples of the " C_{7-19} aralkyl" in the above " C_{7-19} aralkyl which may have substituents" include benzyl, phenethyl, diphenylmethyl, triphenylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, 2,2-diphenylethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl. Benzyl is

particularly preferable.

Examples of the "substituents" in the above "C₇₋₁₉ aralkyl which may have substituents" include halogen atom (e.g. fluorine, chlorine, bromine, iodine, etc.), C₁₋₃ alkylene dioxy (e.g. methylenedioxy, ethylenedioxy, etc.),
5 nitro, cyano, optionally halogenated C₁₋₆ alkyl, optionally halogenated C₃₋₆ cycloalkyl, optionally halogenated C₁₋₆ alkoxy, optionally halogenated C₁₋₆ alkylthio, hydroxy, amino, mono-C₁₋₆ alkylamino (e.g. methylamino, ethylamino,
10 propylamino, isopropylamino, butylamino, etc.), di-C₁₋₆ alkylamino (e.g. dimethylamino, diethylamino, dipropylamino, dibutylamino, ethylmethylamino, etc.), amino-C₁₋₆ alkyl (e.g. aminomethyl, aminoethyl, aminopropyl, aminobutyl, etc.), mono-C₁₋₆ alkylamino-C₁₋₆
15 alkyl (e.g. methylaminomethyl, ethylaminomethyl, propylaminomethyl, isopropylaminoethyl, butylaminoethyl, etc.), di-C₁₋₆ alkylamino-C₁₋₆ alkyl (e.g. dimethylaminomethyl, diethylaminomethyl, dipropylaminomethyl, diisopropylaminoethyl,
20 dibutylaminoethyl, etc.), formyl, carboxy, carbamoyl, thiocarbamoyl, optionally halogenated C₁₋₆ alkyl-carbonyl, C₁₋₆ alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl, etc.), mono-C₁₋₆ alkyl-carbamoyl (e.g., methylcarbamoyl,
25 ethylcarbamoyl, etc.), di-C₁₋₆ alkyl-carbamoyl (e.g. dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, etc.), optionally halogenated C₁₋₆ alkylsulfonyl, formylamino, optionally halogenated C₁₋₆ alkyl-carboxamide, C₁₋₆ alkoxy-carboxamide (e.g.
30 methoxycarboxamide, ethoxycarboxamide, propoxycarboxamide, butoxycarboxamide, etc.), C₁₋₆ alkylsulfonylamino (e.g. methylsulfonylamino, ethylsulfonylamino, etc.), C₁₋₆ alkyl-carbonyloxy (e.g. acetoxy, propanoyloxy, etc.), C₁₋₆ alkoxy-carbonyloxy (e.g.
35 methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, butoxycarbonyloxy, etc.) mono-C₁₋₆

alkyl-carbamoyloxy (e.g. methylcarbamoyloxy, ethylcarbamoyloxy, etc.), di-C₁₋₆ alkyl-carbamoyloxy (e.g. dimethylcarbamoyloxy, diethylcarbamoyloxy, etc.). The number of substituents is, for instance, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

As "optionally halogenated C₁₋₆ alkyl", "optionally halogenated C₃₋₆ cycloalkyl", "optionally halogenated C₁₋₆ alkoxy" and "optionally halogenated C₁₋₆ alkylthio", those exemplified as "substituents" in the above "cyclic group which may have substituents" can be used respectively.

Examples of the above "optionally halogenated C₁₋₆ alkylcarbonyl" include C₁₋₆ alkyl-carbonyl (e.g. acetyl, propanoyl, butanoyl, pentanoyl, hexanoyl, etc.) which may have 1 to 5, preferably 1 to 3, halogen atoms (e.g., fluorine, chlorine, bromine, iodine, etc.). Concrete examples include acetyl, monochloroacetyl, trifluoroacetyl, trichloroacetyl, propanoyl, butanoyl, pentanoyl, hexanoyl.

Examples of the above "optionally halogenated C₁₋₆ alkylsulfonyl" include C₁₋₆ alkylsulfonyl (e.g. methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, sec-butylsulfonyl, tert-butylsulfonyl, etc.) which may have 1 to 5, preferably 1 to 3, halogen atoms (e.g., fluorine, chlorine, bromine, iodine, etc.). Concrete examples include methylsulfonyl, difluoromethylsulfonyl, trifluoromethylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, 4,4,4-trifluorobutylsulfonyl, pentylsulfonyl, hexylsulfonyl.

Examples of the above "optionally halogenated C₁₋₆ alkyl-carboxamide" include C₁₋₆ alkyl-carboxamide (e.g. acetamide, propanamide, butanamide, etc.) which may have 1 to 5, preferably 1 to 3, halogen atoms (e.g. fluorine, chlorine, bromine, iodine, etc.). Concrete examples include acetamide, trifluoroacetamide, propanamide,

butanamide.

Examples of "C₆₋₁₄ aryloxy" in the above "C₆₋₁₄ aryloxy which may have substituents" include phenyloxy, 1-naphthyloxy, 2-naphthyloxy.

5 Examples of "C₇₋₁₉ aralkyloxy" in the above "C₇₋₁₉ aralkyloxy which may have substituents" include benzyloxy, phenethyloxy, diphenylmethyloxy, triphenylmethyloxy, 1-naphthylmethyloxy, 2-naphthylmethyloxy, 2,2-diphenylethyloxy, 3-phenylpropyloxy, 4-phenylbutyloxy,
10 5-phenylpentyloxy.

Examples of "C₆₋₁₄ arylcarbamoyl" in the above "C₆₋₁₄ arylcarbamoyl which may have substituents" include phenylcarbamoyl, 1-naphthylcarbamoyl, 2-naphthylcarbamoyl.

15 As the "substituents" in the "C₆₋₁₄ aryloxy which may have substituents", "C₇₋₁₉ aralkyloxy which may have substituents" and "C₆₋₁₄ aryl-carbamoyl which may have substituents", those exemplified for "substituents" in the above "C₇₋₁₉ aralkyl which may have substituents" can be used.

20 The number of substituents is, for instance, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

Examples of the "5 to 7 membered saturated cyclic amino" in the above "5 to 7 membered saturated cyclic amino which may have substituents" include morpholino, thiomorpholino, piperazin-1-yl, piperidino, pyrrolidin-1-yl. The "5 to 7 membered saturated cyclic amino" can be condensed with a benzene ring.

25 Examples of "substituents" in the "5 to 7 membered saturated cyclic amino which may have substituents" include
30 oxo, optionally halogenated C₁₋₆ alkyl, optionally halogenated C₁₋₆ alkyl-carbonyl, optionally halogenated C₁₋₆ alkylsulfonyl, C₆₋₁₄ aryl which may have substituents, C₇₋₁₉ aralkyl which may have substituents, C₆₋₁₄ aryl-carbonyl
35 which may have substituents, 5 to 10 membered aromatic heterocyclic group which may have substituents, 5 to 8

membered monocyclic non-aromatic heterocyclic group (e.g., piperidino, piperazinyl, pyrrolidinyl, dihydropyridyl, etc.). The number of substituents is, for instance, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

Here, as "optionally halogenated C₁₋₆ alkyl" and "C₇₋₁₉ aralkyl which may have substituents", those exemplified as "substituents" in the above "cyclic group which may have substituents" can be used.

As "optionally halogenated C₁₋₆ alkyl-carbonyl" and "optionally halogenated C₁₋₆ alkylsulfonyl", those exemplified as "substituents" in the above "C₇₋₁₉ aralkyl which may have substituents" can be used.

Examples of the "C₆₋₁₄ aryl" in the "C₆₋₁₄ aryl which may have substituents" include phenyl, 1-naphthyl, 2-naphthyl, 2-indenyl, 2-anthryl. Phenyl is especially preferable.

As the substituents in the "C₆₋₁₄ aryl which may have substituents", those exemplified as "substituents" in the above "C₇₋₁₉ aralkyl which may have substituents" can be used.

The number of substituents is, for instance, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

Examples of the "C₆₋₁₄ aryl-carbonyl" in the "C₆₋₁₄ aryl-carbonyl which may have substituents" include benzoyl, 1-naphthoyl, 2-naphthoyl.

As the "substituents" in the "C₆₋₁₄ aryl-carbonyl which may have substituents", those exemplified as "substituents" in the above "C₇₋₁₉ aralkyl which may have substituents" can be used. The number of substituents is, for instance, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

Examples of "5 to 10 membered aromatic heterocyclic groups" in "5 to 10 membered aromatic heterocyclic groups which may have substituents" include 5 to 10 membered (monocyclic or bicyclic) aromatic heterocyclic groups

containing 1 or 2 kinds of, preferably 1 to 4 hetero atoms selected from nitrogen, sulfur and oxygen atom in addition to carbon atoms. Concrete examples include 2- or 3-thienyl; 2-, 3- or 4-pyridyl; 2- or 3-furyl; 2-, 4- or 5-thiazolyl; 2-, 4- or 5-oxazolyl; 1-, 3- or 4-pyrazolyl; 2-pyrazinyl; 2-, 4- or 5-pyrimidinyl; 1-, 2- or 3-pyrrolyl; 1-, 2- or 4-imidazolyl; 3- or 4-pyridazinyl; 3-isothiazolyl; 3-isoxazolyl; 1,2,4-oxadiazol-5-yl; 1,2,4-oxadiazol-3-yl; 2-, 3-, 4-, 5- or 8-quinolyl; 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl; 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl; 1-, 2-, 4- or 5-isoindolyl; 1-, 5- or 6-phthalazinyl; 2-, 3- or 5-quinoxaliny; 2-, 3-, 4-, 5- or 6-benzofuranyl; 2-, 4-, 5- or 6-benzothiazolyl; 1-, 2-, 4-, 5- or 6-benzimidazolyl.

Examples of the "substituents" in the "5 to 10 membered aromatic heterocyclic groups which may have substituents" include halogen atom (e.g. fluorine, chlorine, bromine and iodine, etc.), C_{1-3} alkylenedioxy (e.g. methylenedioxy, ethylenedioxy, etc.), nitro, cyano, optionally halogenated C_{1-6} alkyl, C_{6-14} aryloxy- C_{1-6} alkyl (e.g. phenoxymethyl, etc.), C_{1-6} alkyl- C_{6-14} aryl- C_{2-6} alkenyl (e.g. methylphenylethenyl, etc.), optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, C_{7-19} aralkyl which may have substituents, hydroxy, C_{6-14} aryloxy which may have substituents, C_{7-19} aralkyloxy which may have substituents, amino, amino- C_{1-6} alkyl (e.g. aminomethyl, aminoethyl, aminopropyl, aminobutyl, etc.), mono- C_{1-6} alkylamino (e.g. methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), di- C_{1-6} alkylamino (e.g. dimethylamino, diethylamino, dipropylamino, dibutylamino, ethylmethylamino, etc.), mono- C_{1-6} alkylamino- C_{1-6} alkyl (e.g. methylaminomethyl, ethylaminomethyl, propylaminomethyl, isopropylaminoethyl, butylaminoethyl, etc.), di- C_{1-6} alkylamino- C_{1-6} alkyl (e.g. dimethylaminomethyl, diethylaminomethyl,

dipropylaminomethyl, diisopropylaminoethyl, dibutylaminoethyl, etc.), 5 to 7 membered saturated cyclic amino, acyl, acylamino, acyloxy. The number of substituents is, for instance, 1 to 5, preferably 1 to 3.

5 When the number of substituents is 2 or more, each substituents can be the same or different.

Here, as "optionally halogenated C₁₋₆ alkyl", "optionally halogenated C₃₋₆ cycloalkyl", "optionally halogenated C₁₋₆ alkoxy", "optionally halogenated C₁₋₆ alkylthio", "C₇₋₁₉ aralkyl which may have substituents", "C₆₋₁₄ aryloxy which may have substituents", "C₇₋₁₉ aralkyloxy which may have substituents", those exemplified as the "substituent" in the above "cyclic group which may have substituents" can be used respectively.

15 As a "5 to 7 membered saturated cyclic amino", those exemplified as "5 to 7 membered saturated cyclic amino" regarding "5 to 7 membered saturated cyclic amino which may have substituents" which is a "substituent" in the above "5 to 7 membered saturated cyclic amino which may have substituents" can be used.

20 Examples of the above "acyl" include acyl of the formulae : -CO-R³, -CO-OR³, -CO-NR³R⁴, -CS-NR³R⁴, -SO₂-R^{3a}, -SO-R^{3a}, -PO(-OR³)-OR⁴ or -PO₂-R^{3a} wherein R³ is (i) hydrogen atom, (ii) a hydrocarbon group which may have substituents, or (iii) a heterocyclic group which may have substituents; R^{3a} is (i) a hydrocarbon group which may have substituents, or (ii) a heterocyclic group which may have substituents; R⁴ is hydrogen atom or C₁₋₆ alkyl; R³ and R^{3a}, together with the adjacent nitrogen atom, can form a nitrogen-containing hetero ring which may have substituents.

30 Examples of the "hydrocarbon group" in "hydrocarbon group which may have substituents" for R³ or R⁴ include straight-chain or cyclic hydrocarbon groups (e.g. alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, etc.). Among these, C₁₋₁₉ straight chain or cyclic hydrocarbon groups as

shown below are preferable.

a) C₁₋₆ alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.);

5 b) C₂₋₆ alkenyl (e.g., vinyl, allyl, isopropenyl, 2-butenyl, etc.);

c) C₂₋₆ alkynyl (e.g. ethynyl, propargyl, 2-butyne, etc.);

10 d) C₃₋₆ cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.); the C₃₋₆ cycloalkyl can be condensed with one benzene ring;

e) C₆₋₁₄ aryl (e.g. phenyl, 1-naphthyl, 2-naphthyl, 2-indenyl, 2-anthryl, etc.), preferably phenyl;

15 f) C₇₋₁₉ aralkyl (e.g. benzyl, phenethyl, diphenylmethyl, triphenylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, 2,3-diphenylethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl, etc.), preferably benzyl.

The "hydrocarbon groups" are preferably C₁₋₆ alkyl, C₆₋₁₄ aryl, C₇₋₁₉ aralkyl, etc.

20

Examples of the "substituent" in "hydrocarbon groups which may have substituents" include halogen atom (e.g. fluorine, chlorine, bromine, iodine, etc.), C₁₋₃ alkylenedioxy (e.g. methylenedioxy, ethylenedioxy, etc.),
25 nitro, cyano, optionally halogenated C₁₋₆ alkoxy, optionally halogenated C₁₋₆ alkylthio, hydroxy, amino, mono-C₁₋₆ alkylamino (e.g. methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), di-C₁₋₆ alkylamino (e.g. dimethylamino, diethylamino,
30 dipropylamino, dibutylamino, ethylmethylamino, etc.), formyl, carboxy, carbamoyl, thiocarbamoyl, optionally halogenated C₁₋₆ alkyl-carbonyl, C₁₋₆ alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl, etc.), 5 to 10 membered aromatic
35 heterocyclic groups which may have substituents, C₆₋₁₄ aryl-carbonyl which may have substituents, C₆₋₁₄

aryloxy-carbonyl which may have substituents, C_{7-19}
aralkyloxy-carbonyl which may have substituents, 5 to 6
membered hetero ring-carbonyl which may have substituents,
mono- C_{1-6} alkyl-carbamoyl (e.g. methylcarbamoyl,
5 ethylcarbamoyl, etc.), di- C_{1-6} alkyl-carbamoyl (e.g.
dimethylcarbamoyl, diethylcarbamoyl,
ethylmethylcarbamoyl, etc.), C_{6-14} aryl-carbamoyl which may
have substituents, 5 to 6 membered hetero ring-carbamoyl
which may have substituents, optionally halogenated C_{1-6}
10 alkylsulfonyl, C_{6-14} arylsulfonyl which may have
substituents, formylamino, C_{1-6} alkyl-carbonyloxy (e.g.
acetoxo, propanoyloxy, etc.), C_{6-14} aryl-carbonyloxy which
may have substituents, C_{1-6} alkoxy-carbonyloxy (e.g.
methoxycarbonyloxy, ethoxycarbonyloxy,
15 propoxycarbonyloxy, butoxycarbonyloxy, etc.), mono- C_{1-6}
alkyl-carbamoyloxy (e.g. methylcarbamoyloxy,
ethylcarbamoyloxy, etc.), di- C_{1-6} alkyl-carbamoyloxy (e.g.
dimethylcarbamoyloxy, diethylcarbamoyloxy, etc.), C_{6-14}
aryl-carbamoyloxy which may have substituents,
20 nicotinoyloxy. The number of substituents is, for
instance, 1 to 5, preferably 1 to 3. When the number of
substituents is 2 or more, each substituents can be the same
or different.

Here, as "optionally halogenated C_{1-6} alkoxy",
25 "optionally halogenated C_{1-6} alkylthio" and " C_{6-14} aryl-
carbamoyl which may have substituents", those exemplified
as a "substituent" in the above "cyclic group which may have
substituents" can be used.

As "optionally halogenated C_{1-6} alkyl-carbonyl" and
30 "optionally halogenated C_{1-6} alkylsulfonyl", those
exemplified as a "substituent" in the above " C_{7-19} aralkyl
which may have substituents" can be used.

As the above "5 to 10 membered aromatic heterocyclic
groups which may have substituents" and " C_{6-14} aryl-carbonyl
35 which may have substituents", those exemplified as
"substituent" in the above "5 to 7 membered saturated cyclic

amino which may have substituents" can be used.

Examples of "C₆₋₁₄ aryloxy-carbonyl" in "C₆₋₁₄ aryloxy-carbonyl which may have substituents" include phenyloxycarbonyl, 1-naphthyloxycarbonyl, 2-
5 naphthyloxycarbonyl.

Examples of "C₇₋₁₉ aralkyloxy-carbonyl" in "C₇₋₁₉ aralkyloxy-carbonyl which may have substituents" include benzyloxycarbonyl, phenethyloxycarbonyl, diphenylmethyloxycarbonyl, triphenylmethyloxycarbonyl,
10 1-naphthylmethyloxycarbonyl, 2-naphthylmethyloxycarbonyl, 2,2-diphenylethyloxycarbonyl, 3-phenylpropyloxycarbonyl, 4-phenylbutyloxycarbonyl, 5-phenylpentyloxycarbonyl.

Examples of "5 to 6 membered hetero ring-carbonyl" in
15 the above "5 to 6 membered hetero ring-carbonyl which may have substituents" include nicotinoyl, isonicotinoyl, 2-thenoyl, 3-thenoyl, 2-furoyl, 3-furoyl, molpholinocarbonyl, pepiridinocarbonyl, pyrrolidin-1-ylcarbonyl.

20 Examples of the "5 to 6 membered hetero ring-carbamoyl" in the above "5 to 6 membered hetero ring-carbamoyl which may have substituents" include molpholinocarbamoyl, pepiridinocarbamoyl, 2-pyridylcarbamoyl, 3-pyridylcarbamoyl, 4-
25 pyridylcarbamoyl, 2-thienylcarbamoyl, 3-thienylcarbamoyl.

Examples of "C₆₋₁₄ arylsulfonyl" in the above "C₆₋₁₄ arylsulfonyl which may have substituents" include phenylsulfonyl, 1-naphthylsulfonyl, 2-naphthylsulfonyl.

30 Examples of "C₆₋₁₄ aryl-carbonyloxy" in the above "C₆₋₁₄ aryl-carbonyloxy which may have substituents" include benzoyloxy, 1-naphthoyloxy, 2-naphthoyloxy.

Examples of "C₆₋₁₄ aryl-carbamoyloxy" in the above "C₆₋₁₄ aryl-carbamoyloxy which may have substituents" include
35 phenylcarbamoyloxy, naphthylcarbamoyloxy.

As the "substituents" in the above "C₆₋₁₄ aryloxy-

carbonyl which may have substituents", "C₇₋₁₉ aralkyloxy-carbonyl which may have substituents", "5 to 6 membered hetero ring-carbonyl which may have substituents", "5 to 6 membered hetero ring-carbamoyl which may have substituents", "C₆₋₁₄ arylsulfonyl which may have substituents", "C₆₋₁₄ aryl-carbonyloxy which may have substituents" and "C₆₋₁₄ aryl-carbamoyloxy which may have substituents", those exemplified as "substituents" in the above "C₇₋₁₉ aralkyl which may have substituents" can be mentioned. The number of the substituents is, for instance, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

Examples of "heterocyclic groups" in the "heterocyclic groups which may have substituents" for R³ or R^{3a} include a 5 to 14 membered (monocyclic, bicyclic or tricyclic) hetero ring containing 1 or 2 kinds of, 1 to 4 hetero atoms selected from nitrogen, sulfur and oxygen atom in addition to carbon atoms. Preferably, univalent groups formed by removing an optional one hydrogen atom from (i) an aromatic hetero ring, (ii) a 5 to 10 membered non-aromatic hetero ring, or (iii) a 7 to 10 membered hetero-bridge ring, can be mentioned.

Here, examples of the "aromatic hetero ring" include a 5 to 14 membered, preferably 5 to 10 membered, aromatic hetero ring containing one or more hetero atom (e.g. 1 to 4) selected from nitrogen, sulfur and oxygen atom in addition to carbon atoms.

Concrete examples include aromatic hetero rings such as thiophene, furan, pyrrole, imidazole, pyrazole, thiazole, isothiazole, oxazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, 1,2,4-oxadiazole, 1,3,4-oxadiazole, 1,2,4-thiadiazole, 1,3,4-thiadiazole, furazan, benzothiophene, benzofuran, benzimidazole, benzoxazole, benzothiazole, benzisothiazole,

naphtho[2,3-b]thiophene, phenoxathiin, indole, isoindole, 1H-indazole, purine, 4H-quinolidine, isoquinoline, quinoline, phthalazine, naphthylidine, quinoxaline, quinazoline, cinnoline, carbazole, β -carboline, phenanthridine, acridine, phenazinephenothiadine, phenoxazine, phthalimide, etc.; or a ring formed by condensing these rings (preferably monocyclic rings) with one to multiple (preferably 1 or 2) aromatic rings (e.g. benzene ring, etc.).

10 Examples of "5 to 10 membered non-aromatic hetero rings" include 2- or 3-pyrroline, pyrrolidine, 2- or 3-imidazoline, 2-oxazoline, oxazolidine, 2- or 3-pyrazoline, pyrazolidine, 2-thiazoline, piperidine, piperazine, hexamethylenimine, morpholine, thiomorpholine.

15 Examples of "7 to 10 membered hetero-bridge rings" include quinuclidine, 7-azabicyclo[2.2.1]heptane.

 The "hetero cyclic groups" are preferably 5 to 10 membered (monocyclic or bicyclic) heterocyclic groups containing 1 or 2 kinds of, preferably 1 to 4, hetero atoms selected from nitrogen, sulfur and oxygen atom in addition to carbon atoms. Concretely examples include aromatic heterocyclic groups such as 2- or 3-thienyl; 2-, 3- or 4-pyridyl; 2- or 3-furyl; 2-, 4- or 5-thiazolyl; 2-, 4- or 5-oxazolyl; 1-, 3- or 4-pyrazolyl; 2-pyrazinyl; 2-, 4- or 5-pyrimidinyl; 1-, 2- or 3-pyrrolyl; 1-, 2- or 4-imidazolyl; 3- or 4-pyridazinyl; 3-isothiazolyl; 3-isoxazolyl; 1,2,4-oxadiazol-5-yl; 1,2,4-oxadiazol-3-yl; 2-, 3-, 4-, 5- or 8-quinolyl; 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl; 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl; 1-, 2-, 4- or 5-isoindolyl; 1-, 5- or 6-phthalazinyl; 2-, 3- or 5-quinoxalinyll; 2-, 3-, 4-, 5- or 6-benzofuranyl; 2-, 3-, 4-, 5- or 6-benzothienyl; 2-, 4-, 5- or 6-benzothiazolyl; 1-, 2-, 4-, 5- or 6-benzimidazolyl; and non-aromatic heterocyclic groups such as 1-, 2- or 3-pyrrolidinyl; 1-, 2-, 4- or 5-imidazolidinyl; 2- or 4-imidazolinyl; 2-, 3- or 4-pyrazolidinyl; piperidino; 2-, 3- or 4-piperidyl; 1-

or 2-piperazinyl; morpholino.

As the "substituents" in the "heterocyclic groups which may have substituents", those exemplified as "substituents" in the above "5 to 10 membered aromatic
5 heterocyclic groups which may have substituents" can be used. The number of substituents is, for instance, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

Examples of "C₁₋₆ alkyl" for R⁴ include methyl, ethyl,
10 propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl.

Examples of "nitrogen-containing hetero ring" in the "nitrogen-containing hetero ring which may have substituents" formed by R³ and R⁴ together with the adjacent
15 nitrogen atoms, include a 5 to 7 membered nitrogen-containing hetero ring which contains at least one nitrogen atom in addition to carbon atoms and may contain 1 to 3 hetero atoms selected from nitrogen, sulfur and oxygen atom. The "nitrogen-containing hetero rings" are preferably
20 piperidine, morpholine, thiomorpholine, piperazine, pyrrolidine, etc.

As the "substituents" in the "nitrogen-containing hetero ring which may have substituents", those exemplified as "substituents" in the above "5 to 10 membered aromatic
25 heterocyclic groups which may have substituents" can be used. The number of substituents is, for instance, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

The "acyl" is preferably formyl, carboxy, carbamoyl,
30 optionally halogenated C₁₋₆ alkyl-carbonyl (e.g. acetyl, etc.), C₁₋₆ alkoxy-carbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl, etc.), C₆₋₁₄ aryl-carbonyl which may have substituents (e.g. benzoyl, 1-naphthoyl, 2-naphthoyl, etc.), C₆₋₁₄ aryloxy-carbonyl which may have substituents (e.g.
35 phenyloxycarbonyl, 1-naphthyloxycarbonyl, 2-

naphthyloxycarbonyl; etc.), C_{7-19} aralkyloxy-carbonyl which may have substituents (e.g. benzyloxycarbonyl, phenethyloxycarbonyl, etc.), a 5 to 6 membered hetero ring-carbonyl which may have substituents (e.g. 5 nicotinoyl, etc.), mono- C_{1-6} alkyl-carbamoyl (e.g. methylcarbamoyl, ethylcarbamoyl, etc.), di- C_{1-6} alkyl-carbamoyl (e.g. dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, etc.), C_{6-14} aryl-carbamoyl which may have substituents (e.g. phenylcarbamoyl, 4-methoxyphenylcarbamoyl, 3,4-dimethoxyphenylcarbamoyl, etc.), aromatic hetero ring-carbamoyl which may have substituents (e.g. 2-pyridinylcarbamoyl, 2-quinolinylcarbamoyl etc.), optionally halogenated C_{1-6} alkylsulfonyl (e.g. methylsulfonyl, etc.), C_{6-14} 15 arylsulfonyl which may have substituents (e.g. phenylsulfonyl etc.), etc.

Here, as "optionally halogenated C_{1-6} alkyl-carbonyl" and "optionally halogenated C_{7-19} aralkylsulfonyl", those exemplified as "substituents" in the above " C_{7-19} aralkyl 20 which may have substituents" can be used.

As " C_{6-14} aryl-carbonyl which may have substituents", "substituents" in the above "5 to 7 membered saturated cyclic amino which may have substituents" can be used.

As " C_{6-14} aryloxy-carbonyl which may have 25 substituents", " C_{7-19} aralkyloxy-carbonyl which may have substituents", "5 to 6 membered hetero ring-carbonyl which may have substituents", "aromatic hetero ring-carbamoyl which may have substituents" and " C_{6-14} arylsulfonyl which may have substituents", those exemplified as 30 "substituents" in the above "hydrocarbon groups which may have substituents" can be used.

As " C_{6-14} aryl-carbamoyl which may have substituents", those exemplified as "substituents" in the above "cyclic group which may have substituents" can be used.

35

Examples of the above "acylamino" include amino which

is substituted by 1 or 2 of the above "acyl". Preferably, acylamino of the formulae : $-NR^5-COR^6$, $-NR^5-COOR^{6a}$, $-NR^5-SO_2R^{6a}$, $-NR^5-CONR^{6a}R^{6b}$, $-PO(-OR^5)-OR^6$, or $-PO_2-R^6$ wherein R^5 is hydrogen atom or C_{1-6} alkyl; R^6 has the same meaning as the above R^3 ; R^{6a} has the same meaning as the above R^{3a} ; and R^{6b} has the same meaning as R^4], can be mentioned.

As " C_{1-6} alkyl" for R^5 , the same one as in " C_{1-6} alkyl" for the above R^4 can be mentioned.

The "acylamino" is preferably formylamino, optionally halogenated C_{1-6} alkyl-carboxamide (e.g. methylcarboxamide, trifluoromethylcarboxamide, isopropylcarboxamide, etc.), C_{6-14} aryl-carboxamide which may have substituents (e.g. phenylcarboxamide, 2-methoxyphenylcarboxamide, 4-methoxyphenylcarboxamide, etc.), N-(C_{6-14} aryl-carbonyl which may have substituents)-N- C_{1-6} alkylamino (e.g. N-4-methoxybenzoyl-N-methylamino, etc.), C_{7-19} aralkyl-carboxamide which may have substituents (e.g. benzylcarboxamide, etc.), aromatic hetero ring-carboxamide which may have substituents (e.g. benzothiophen-2-ylcarboxamide, etc.), optionally halogenated C_{1-6} alkoxy-carboxamide (e.g. methoxycarboxamide, ethoxycarboxamide, propoxycarboxamide, butoxycarboxamide, etc.), C_{6-14} arylamino-carbonylamino which may have substituents (e.g. phenylaminocarbonylamino, etc.), optionally halogenated C_{1-6} alkylsulfonylamino (e.g. methylsulfonylamino, trifluoromethylsulfonylamino, ethylsulfonylamino, etc.), C_{6-14} arylsulfonylamino which may have substituents (e.g. 4-methoxyphenylsulfonylamino, etc.).

Here, as "substituents" in " C_{6-14} aryl-carboxamide which may have substituents", "N-(C_{6-14} aryl-carbonyl which may have substituents)-N- C_{1-6} arylalkylamino", " C_{7-19} aralkyl-carboxamide which may have substituents", "aromatic hetero ring-carboxamide which may have substituents", " C_{6-14} arylamino-carbonylamino which may

have substituents" and "C₆₋₁₄ arylsulfonylamino which may have substituents", those exemplified as "substituents" in the above "C₇₋₁₉ aralkyl which may have substituents" can be mentioned. The number of substituents is, for instance,
5 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

Examples of the above "acyloxy" include oxy substituted by one of the above "acyl". Preferably,
10 acyloxy of the formulae : -O-COR⁷, -O-COOR⁷, -O-CONHR⁷, -PO(OH)-OR⁷ or -PO₂-R⁷ wherein R⁷ has the same meaning as the above R³, can be mentioned.

The "acyloxy" is preferably optionally halogenated C₁₋₆ alkyl-carbonyloxy (e.g. acetoxy, propanoyloxy, etc.),
15 C₆₋₁₄ aryl-carbonyloxy which may have substituents (e.g. benzoyloxy, 4-methoxybenzoyloxy, etc.), optionally halogenated C₁₋₆ alkoxy-carbonyloxy (e.g. methoxycarbonyloxy, trifluoromethoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy,
20 butoxycarbonyloxy, etc.), mono-C₁₋₆ alkyl-carbamoyloxy (e.g. methylcarbamoyloxy, ethylcarbamoyloxy, etc.), di-C₁₋₆ alkyl-carbamoyloxy (e.g. dimethylcarbamoyloxy, diethylcarbamoyloxy, etc.), C₆₋₁₄ aryl-carbamoyloxy which may have substituents (e.g. phenylcarbamoyloxy,
25 naphthylcarbamoyloxy, etc.), nicotinyloxy, etc.

As "substituents" in "C₆₋₁₄ aryl-carbonyloxy which may have substituents" and "C₆₋₁₄ aryl-carbamoyloxy which may have substituents", those exemplified as "substituents" in the above "C₇₋₁₉ aralkyl which may have substituents" can
30 be mentioned. The number of substituents is, for instance, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

Examples of the "5 to 7 membered non-aromatic
35 heterocyclic groups which may have substituents", which is "substituents" in "cyclic group which may have

substituents" for Ar¹, include 4,5-dihydro-1,3-oxazol-2-yl, 4,5-dihydro-1,3-thiazol-2-yl, 4,5-dihydro-1H-2-imidazolyl. As "substituents" in the "5 to 7 membered non-aromatic heterocyclic groups which may have substituents", those exemplified as "substituents" in the above "5 to 7 membered saturated cyclic amino which may have substituents" can be used.

As "acyl", "acyloxy" and "acylamino", which are "substituents" in the "cyclic group which may have substituents" for Ar¹, those exemplified as "substituents" in the above "5 to 10 membered aromatic heterocyclic groups which may have substituents" can be used.

Regarding "aromatic hetero ring-C₁₋₆ alkoxy" which is "substituents" in the "cyclic group which may have substituents" for Ar¹, as "aromatic hetero ring", those exemplified as the above R³ can be used. Examples of "C₁₋₆ alkoxy" include methoxy, ethoxy, propoxy, butoxy, pentyloxy.

"Substituents" in the "cyclic group which may have substituents" for Ar¹ are preferably halogen atom (preferably fluorine, chlorine and bromine, etc.); nitro; C₁₋₃ alkylenedioxy (preferably methylenedioxy, etc.); optionally halogenated C₁₋₆ alkyl (preferably, methyl, ethyl, propyl, trifluoromethyl, etc.); hydroxy-C₁₋₆ alkyl (preferably hydroxymethyl, etc.); optionally halogenated C₃₋₆ cycloalkyl (preferably cyclohexyl, etc.); optionally halogenated C₁₋₆ alkoxy (preferably methoxy, ethoxy, etc.); optionally halogenated C₁₋₆ alkylthio (preferably methylthio, etc.); hydroxy; C₇₋₁₉ aralkyloxy which may have substituents (preferably, 1 to 3 substituents selected from halogen atom, optionally halogenated C₁₋₆ alkyl, optionally halogenated C₁₋₆ alkoxy, optionally halogenated C₁₋₆ alkylthio, etc.) (preferably benzyloxy, 4-methoxybenzyloxy, 3-methoxybenzyloxy, 4-fluorobenzyloxy, 4-methylthiobenzyloxy, 4-ethylbenzyloxy, etc.); C₆₋₁₄

aryloxy which may have substituents (preferably, 1 to 3 optionally halogenated C₁₋₆ alkoxy, etc.) (preferably phenyloxy, 4-methoxyphenyloxy, etc.); amino; mono-C₁₋₆ alkylamino (preferably methylamino, etc.); di-C₁₋₆ alkylamino (preferably dimethylamino, etc.); 5 to 7 membered saturated cyclic amino which may have substituents (preferably 1 to 3 oxo) and may be condensed with a benzene ring (preferably 1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl, etc.); 5 to 7 membered non-aromatic heterocyclic groups which may have substituents (preferably 4,5-dihydro-1,3-oxazol-2-yl, etc.); formyl; carboxy; C₆₋₁₄ aryl-carbonyl which may have substituents (preferably benzoyl, etc.); C₆₋₁₄ aryl-carbamoyl which may have substituents (preferably, 1 to 3 optionally halogenated C₁₋₆ alkoxy, etc.) (preferably, phenylcarbamoyl, 4-methoxyphenylcarbamoyl, 3,4-dimethoxyphenylcarbamoyl, etc.); aromatic hetero ring-carbamoyl which may have substituents (preferably 2-pyridinylcarbamoyl, 2-quinolinylcarbamoyl, etc.); C₁₋₆ alkoxy-carbonyl (preferably methoxycarbonyl, ethoxycarbonyl, etc.); optionally halogenated C₁₋₆ alkyl-carboxamide (preferably methylcarboxamide, trifluoromethylcarboxamide, isopropylcarboxamide, etc.); C₆₋₁₄ aryl-carboxamide which may have substituents (preferably, 1 to 3 optionally halogenated C₁₋₆ alkoxy, etc.) (preferably phenylcarboxamide, 2-methoxyphenylcarboxamide, 4-methoxyphenylcarboxamide, etc.); C₇₋₁₉ aralkyl-carboxamide which may have substituents (preferably benzylcarboxamide, etc.); aromatic hetero ring-carboxamide which may have substituents (preferably benzothiophen-2-ylcarboxamide, etc.); N-(C₆₋₁₄ aryl-carbonyl which may have substituents (preferably, 1 to 3 optionally halogenated C₁₋₆ alkoxy, etc.))-N-C₁₋₆ alkylamino (preferably N-4-methoxybenzoyl-N-methylamino, etc.); C₆₋₁₄ arylamino-carbonylamino which may have substituents (preferably phenylaminocarbonylamino, etc.); C₆₋₁₄ arylsulfonylamino which may have substituents (preferably,

1 to 3 optionally halogenated C₁₋₆ alkoxy, etc.) (preferably 4-methoxyphenylsulfonylamino, etc.); C₆₋₁₄ aryl-carbonyloxy which may have substituents (preferably, 1 to 3 optionally halogenated C₁₋₆ alkoxy, etc.) (preferably 4-methoxybenzoyloxy, etc.); oxo; carboxy-C₁₋₆ alkyl (preferably carboxyethyl, etc.); C₁₋₆ alkoxy-carbonyl-C₁₋₆ alkyl (preferably methoxycarbonylmethyl, etc.); C₇₋₁₉ aralkyl which may have substituents (preferably 1 to 3 halogen atom) (preferably benzyl, 2,4-dichlorobenzyl, etc.); aromatic hetero ring-C₁₋₆ alkoxy (preferably 2-quinolylmethoxy, etc.); cyano, etc.

When "cyclic group" in "cyclic group which may have substituents" for Ar¹ is a non-aromatic cyclic hydrocarbon group or a non-aromatic heterocyclic group, C₆₋₁₄ aryl which may have substituents (preferably, 1 to 3 substituents selected from halogen atom, C₁₋₃ alkylenedioxy, optionally halogenated C₁₋₆ alkyl, optionally halogenated C₁₋₆ alkoxy, etc.) (preferably phenyl, 4-fluorophenyl, 1,3-benzodioxol-5-yl, 4-chlorophenyl, 4-methylphenyl, 4-methoxyphenyl), hydroxy, C₇₋₁₉ aralkyloxy-carbonyl (preferably benzyloxycarbonyl), C₇₋₁₉ aralkyl (preferably benzyl), etc., can be used as a preferable substituent.

Ar¹ is preferably phenyl, biphenyl (preferably 4-biphenyl, 2-biphenyl), phenyl-pyridyl (preferably 6-phenyl-3-pyridyl, 5-phenyl-2-pyridyl), phenyl-furyl (preferably 5-phenyl-2-furyl), phenyl-isoxazolyl (preferably 3-phenyl-isoxazol-5-yl), diphenyl-oxazolyl (preferably 2,4-diphenyl-1,3-oxazol-5-yl), pyridyl-phenyl (preferably 4-(4-pyridyl)phenyl, 4-(3-pyridyl)phenyl), phenyl-pyrimidinyl (preferably 2-phenyl-5-pyrimidinyl), benzofuranyl-phenyl (preferably 4-(2-benzofuranyl)phenyl), furyl-phenyl (preferably 4-(2-furyl)phenyl), terphenyl (preferably 4,4'-terphenyl), thienyl-phenyl (preferably 4-(2-thienyl)phenyl), indolyl (preferably 2-indolyl, 3-indolyl), naphthyl-oxadiazolyl

(preferably 3-(2-naphthyl)-1,2,4-oxadiazol-5-yl), benzofuranyl-oxadiazole (preferably 3-(2-benzofuranyl)-1,2,4-oxadiazol-5-yl), benzothienyl (preferably 2-benzothienyl), benzofuranyl (preferably 2-benzofuranyl),
5 fluorenyl (preferably 2-fluorenyl), pyridyl-pyrrolyl (preferably 3-(4-pyridyl)pyrrolyl), thioxanthenyl; each of which may have 1 to 3 (preferably 1 or 2) substituents selected from the group consisting of halogen atom (preferably fluorine, chlorine, bromine, etc.); nitro; C₁₋₃
10 alkylenedioxy (preferably methylenedioxy, etc.); optionally halogenated C₁₋₆ alkyl (preferably methyl, ethyl, propyl, trifluoromethyl, etc.); hydroxy-C₁₋₆ alkyl (preferably hydroxymethyl, etc.); optionally halogenated C₃₋₆ cycloalkyl (preferably cyclohexyl, etc.); optionally
15 halogenated C₁₋₆ alkoxy (preferably methoxy, ethoxy, etc.); optionally halogenated C₁₋₆ alkythio (preferably methylthio, etc.); hydroxy; C₇₋₁₉ aralkyloxy which may have substituents (preferably, 1 to 3 substituents selected from halogen atom, optionally halogenated C₁₋₆ alkyl, optionally
20 halogenated C₁₋₆ alkoxy, optionally halogenated C₁₋₆ alkylthio, etc.) (preferably benzyloxy, 4-methoxybenzyloxy, 3-methoxybenzyloxy, 4-fluorobenzyloxy, 4-methylthiobenzyloxy, 4-ethylbenzyloxy, etc.); C₆₋₁₄ aryloxy which may have substituents (preferably, 1 to 3
25 optionally halogenated C₁₋₆ alkoxy, etc.) (preferably phenyloxy, 4-methoxyphenyloxy, etc.); amino; mono-C₁₋₆ alkylamino (preferably methylamino, etc.); di-C₁₋₆ alkylamino (preferably dimethylamino, etc.); 5 to 7 membered saturated cyclic amino which may have substituents
30 (preferably 1 to 3 oxo) and may be condensed with a benzene ring (preferably 1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl, etc.); 5 to 7 membered non-aromatic heterocyclic groups which may have substituents (preferably 4,5-dihydro-1,3-oxazol-2-yl, etc.); formyl; carboxy; C₆₋₁₄ aryl-
35 carbonyl which may have substituents (preferably benzoyl, etc.); C₆₋₁₄ aryl-carbamoyl which may have substituents

(preferably, 1 to 3 optionally halogenated C₁₋₆ alkoxy, etc.) (preferably phenylcarbamoyl, 4-methoxyphenylcarbamoyl, 3,4-dimethoxyphenylcarbamoyl, etc.); aromatic hetero ring-carbamoyl which may have substituents (e.g. 2-
5 pridinylcarbamoyl, 2-quinolinylcarbamoyl, etc.); C₁₋₆ alkoxy-carbonyl (preferably methoxycarbonyl, ethoxycarbonyl, etc.); optionally halogenated C₁₋₆ alkyl-carboxamide (preferably, methylcarboxamide, trifluoromethylcarboxamide, isopropylcarboxamide, etc.);
10 C₆₋₁₄ aryl-carboxamide which may have substituents (preferably, 1 to 3 optionally halogenated C₁₋₆ alkoxy, etc.) (preferably phenylcarboxamide, 2-methoxyphenylcarboxamide, 4-methoxyphenylcarboxamide, etc.); C₇₋₁₉ aralkyl-carboxamide which may have substituents
15 (preferably benzylcarboxamide, etc.); aromatic hetero ring-carboxamide which may have substituents (preferably benzothiophen-2-ylcarboxamide, etc.); N-(C₆₋₁₄ aryl-carbonyl which may have substituents (preferably, 1 to 3 optionally halogenated C₁₋₆ alkoxy, etc.))-N-C₁₋₆ alkylamino
20 (preferably N-4-methoxybenzoyl-N-methylamino, etc.); C₆₋₁₄ arylamino-carbonylamino which may have substituents (preferably phenylaminocarbonylamino, etc.); C₆₋₁₄ arylsulfonylamino which may have substituents (preferably, 1 to 3 optionally halogenated C₁₋₆ alkoxy, etc.) (preferably
25 4-methoxyphenylsulfonylamino, etc.); C₆₋₁₄ aryl-carbonyloxy which may have substituents (preferably, 1 to 3 optionally halogenated C₁₋₆ alkoxy, etc.) (preferably 4-methoxybenzoyloxy, etc.); oxo; carboxy-C₁₋₆ alkyl (preferably carboxyethyl, etc.); C₁₋₆ alkoxy-carbonyl-C₁₋₆ alkyl (preferably methoxycarbonylmethyl, etc.); C₇₋₁₉
30 aralkyl which may have substituents (preferably 1 to 3 halogen atom) (preferably benzyl, 2,4-dichlorobenzyl, etc.); aromatic hetero ring-C₁₋₆ alkoxy (preferably 2-quinolylmethoxy, etc.); and cyano.

35 Further, preferable examples of Ar¹ include piperidinyl (preferably piperidino), piperazinyl,

pyrrolidinyl, dihydropyridyl, tetrahydropyridyl; each of which may have 1 or 2 substituents selected from the group consisting of oxo, C₆₋₁₄ aryl which may have substituents (preferably, 1 to 3 substituents selected from halogen atom, C₁₋₃ alkylenedioxy, optionally halogenated C₁₋₆ alkyl, optionally halogenated C₁₋₆ alkoxy, etc.) (preferably phenyl, 4-fluorophenyl, 1,3-benzodioxol-5-yl, 4-chlorophenyl, 4-methylphenyl, 4-methoxyphenyl), hydroxy, C₇₋₁₉ aralkyloxy-carbonyl (preferably benzyloxycarbonyl) and C₇₋₁₉ aralkyl (preferably benzyl).

Ar¹ is more preferably, phenyl, biphenyl (preferably 4-biphenyl) or phenyl-pyridyl (preferably 6-phenyl-3-pyridyl, 5-phenyl-2-pyridyl); each of which may have 1 or 2 substituents selected from the group consisting of halogen atom (preferably fluorine, chlorine, bromine, etc.); optionally halogenated C₁₋₆ alkyl (preferably methyl, ethyl, propyl, trifluoromethyl, etc.); optionally halogenated C₁₋₆ alkoxy (preferably methoxy, ethoxy, etc.); C₇₋₁₉ aralkyloxy which may have substituents (preferably, 1 to 3 substituents selected from halogen atom, optionally halogenated C₁₋₆ alkyl, optionally halogenated C₁₋₆ alkoxy, optionally halogenated C₁₋₆ alkylthio, etc.) (preferably benzyloxy, 4-methoxybenzyloxy, etc.); C₆₋₁₄ aryloxy which may have substituents (preferably, 1 to 3 optionally halogenated C₁₋₆ alkoxy, etc.) (preferably phenyloxy, etc.); C₆₋₁₄ aryl-carbonyl which may have substituents (preferably, 1 to 3 optionally halogenated C₁₋₆ alkoxy, etc.) (preferably benzoyl, etc.); C₆₋₁₄ aryl-carbamoyl which may have substituents (preferably, 1 to 3 optionally halogenated C₁₋₆ alkoxy, etc.) (preferably phenylcarbamoyl, 4-methoxyphenylcarbamoyl, 3,4-dimethoxyphenylcarbamoyl, etc.); aromatic hetero ring-carbamoyl which may have substituents (e.g. 2-pyridinylcarbamoyl, 2-quinolinylcarbamoyl, etc.); C₆₋₁₄ aryl-carboxamide which may have substituents (preferably, 1 to 3 optionally halogenated C₁₋₆ alkoxy, etc.) (preferably

phenylcarboxamide, 2-methoxyphenylcarboxamide, 4-methoxyphenylcarboxamide, etc.); C_{7-19} aralkyl-carboxamide which may have substituents (preferably benzylcarboxamide, etc.); aromatic hetero ring-carboxamide (preferably benzothiophen-2-ylcarboxamide, etc.); N-(C_{6-14} aryl-carbonyl which may have substituents (preferably, 1 to 3 optionally halogenated C_{1-6} alkoxy, etc.))-N- C_{1-6} alkylamino (preferably N-4-methoxybenzoyl-N-methylamino, etc.); C_{6-14} arylamino-carbonylamino which may have substituents (preferably phenylaminocarbonylamino, etc.); C_{6-14} arylsulfonylamino which may have substituents (preferably, 1 to 3 optionally halogenated C_{1-6} alkoxy, etc.) (preferably 4-methoxyphenylsulfonylamino, etc.); and C_{6-14} arylcarbonyloxy which may have substituents (preferably, 1 to 3 optionally halogenated C_{1-6} alkoxy, etc.) (preferably 4-methoxybenzoyloxy, etc.).

Further, preferable examples of Ar^1 include piperidino, piperazinyl or pyrrolidinyl; each of which may have 1 or 2 substituents selected from the group consisting of oxo and C_{6-14} aryl (preferably phenyl) which may have substituents [preferably halogen atom (preferably fluorine, chlorine, bromine, etc.), optionally halogenated C_{1-6} alkyl (preferably methyl, ethyl, propyl, trifluoromethyl, etc.) or optionally halogenated C_{1-6} alkoxy (preferably methoxy, ethoxy, etc.)].

The "spacer having a main chain of 1 to 6 atoms" means a space in which 1 to 6 atoms are linked. Here, the "number of atoms in the main chain" is counted so that the number of atoms in the main chain is minimum. For instance, the number of atoms of 1,2-cyclopentylene is counted as 2, and the number of atoms of 1,3-cyclopentylene is counted as 3.

Examples of the "spacer having a main chain of 1 to 6 atoms" include a bivalent group consisting of 1 to 3 species selected from -O-, -S-, -CO-, -SO-, -SO₂-, -NR⁸- (R⁸ is hydrogen atom, optionally halogenated C_{1-6} alkyl,

optionally halogenated C_{1-6} alkyl-carbonyl, optionally halogenated C_{1-6} alkylsulfonyl), bivalent C_{1-6} non-cyclic hydrocarbon groups which may have substituents, and bivalent C_{5-8} monocyclic non-aromatic hydrocarbon groups.

5 Here, as "optionally halogenated C_{1-6} alkyl", those exemplified as "substituents" in the above "cyclic group which may have substituents" can be used.

As "optionally halogenated C_{1-6} alkyl-carbonyl" and "optionally halogenated C_{1-6} alkylsulfonyl", those
10 exemplified as "substituents" in the above " C_{7-19} aralkyl which may have substituents" can be used.

Examples of "bivalent C_{1-6} non-cyclic hydrocarbon groups" in the "bivalent C_{1-6} non-cyclic hydrocarbon groups
15 which may have substituents" include

(1) C_{1-6} alkylene (e.g. $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-(CH(CH_3))_2-$, $-(CH_2)_2C(CH_3)_2-$, $-(CH_2)_3C(CH_3)_2-$, etc.);

(2) C_{2-6} alkenylene (e.g. $-CH=CH-$, $-CH_2-CH=CH-$, $-C(CH_3)_2-CH=CH-$, $-CH_2-CH=CH-CH_2-$, $-CH_2-CH_2-CH=CH-$, $-CH=CH-CH=CH-$, $-CH=CH-CH_2-CH_2-CH_2-$, etc.);

(3) C_{2-6} alkynylene (e.g. $-C\equiv C-$, $-CH_2-C\equiv C-$, $-CH_2-C\equiv C-CH_2-$, etc.)

each of which may have 1 to 5, preferably 1 to 3, halogen
25 atoms (e.g. fluorine, chlorine, bromine, iodine, etc.).

The "bivalent C_{1-6} non-cyclic hydrocarbon groups" may have 1 to 5, preferably 1 to 3 substituents at a substitutable position. Examples of such substituents include halogen atom (e.g. fluorine, chlorine, bromine, iodine, etc.), hydroxy, C_{1-6} alkyl-carbonyloxy (e.g.,
30 acetoxy, etc.).

As the "bivalent C_{5-8} monocyclic non-aromatic hydrocarbon groups", for instance, bivalent groups formed
35 by removing an optional two hydrogen atoms from C_{5-8} cycloalkane or C_{5-8} cycloalkene, can be mentioned. Concret

examples include 1,2-cyclopentylene; 1,3-cyclopentylene; 1,2-cyclohexylene; 1,3-cyclohexylene; 1,4-cyclohexylene; 1,2-cycloheptylene; 1,3-cycloheptylene; 1,4-cycloheptylene; 3-cyclohexen-1,4-ylene; 3-cyclohexen-1,2-ylene; 2,5-cyclohexadien-1,4-ylene. Especially, C₅₋₈ cycloalkylene is preferable.

The "spacer having a main chain of 1 to 6 atoms" is preferably a bivalent group consisting of 1 to 3 species selected from -O-, -S-, -CO-, -SO-, -SO₂-, -NR⁸- (R⁸ has the same meaning as defined above) and optionally halogenated bivalent C₁₋₆ non-cyclic hydrocarbon groups.

Preferred examples of the "spacer having a main chain of 1 to 6 atoms" include

(1) C₁₋₆ alkylene (e.g. -CH₂-, -(CH₂)₂-, -(CH₂)₃-, -(CH₂)₄-, -(CH₂)₅-, -(CH₂)₆-, -CHCH₃-, -C(CH₃)₂-, -CH(CF₃)-, -(CH(CH₃))₂-, -(CF₂)₂-, -(CH₂)₂C(CH₃)₂-, -(CH₂)₃C(CH₃)₂-, etc.);

(2) C₂₋₆ alkenylene (e.g. -CH=CH-, -CH₂-CH=CH-, -CH₂-CF=CH-, -C(CH₃)₂-CH=CH-, -CH₂-CH=CH-CH₂-, -CH₂-CH₂-CH=CH-, -CH=CH-CH=CH-, -CH=CH-CH₂-CH₂-CH₂-, etc.);

(3) C₂₋₆ alkynylene (e.g. -C≡C-, -CH₂-C≡C-, -CH₂-C≡C-CH₂-, etc.);

(4) -(CH₂)_{w1}O(CH₂)_{w2}-, -(CH₂)_{w1}S(CH₂)_{w2}-, -(CH₂)_{w1}CO(CH₂)_{w2}-, -(CH₂)_{w1}SO(CH₂)_{w2}-, -(CH₂)_{w1}SO₂(CH₂)_{w2}-, -(CH₂)_{w1}NR⁸(CH₂)_{w2}-;

(5) -(CH₂)_{w3}CONR⁸(CH₂)_{w4}-, -(CH₂)_{w3}NR⁸CO(CH₂)_{w4}-, -(CH₂)_{w3}SO₂NR⁸(CH₂)_{w4}-, -(CH₂)_{w3}NR⁸SO₂(CH₂)_{w4}-, -(CH₂)_{w3}COO(CH₂)_{w4}-;

(6) -(CH₂)_{w5}NR⁸CONR⁸(CH₂)_{w6}-;

(7) -(CH₂)_{w7}CONR⁸-(CH₂)_{w8}-CONR^{8b}-(CH₂)_{w9}-; -CH=CH-CONR⁸-; -CH=CH-SO₂NR⁸-;

wherein R⁸ has the same meaning as defined above; R^{8b} has the same meaning as R⁸; w1 and w2 is an integer of 0 to 5, and w1 + w2 is 0 to 5; w3 and w4 is an integer of 0 to 4, and w3 + w4 is 0 to 4; w5 and w6 is an integer of 0 to 3, and w5 + w6 is 0 to 3; w7, w8 and w9 is an integer of

0 to 2, and $w7 + w8 + w9$ is 0 to 2.

The "spacer having a main chain of 1 to 6 atoms" for X, is preferably $-(CH_2)_{w1}O(CH_2)_{w2}-$ (symbols have the same meaning as defined above), $-CONR^{8c}-$, $-NR^{8c}CO-$, $-CH=CH-$
5 $CONR^{8c}-$, $-SO_2NR^{8c}-$ (R^8 is hydrogen atom or C_{1-6} alkyl); more preferably $-CONR^{8c}-$, $-NR^{8c}CO-$, $-CH=CH-CONR^{8c}-$, $-SO_2NR^{8c}-$ (R^8 has the same meaning as defined above); especially preferably $-CONH-$, $-NHCO-$, etc.

10 The "spacer having a main chain of 1 to 6 atoms" for Y, is preferably optionally halogenated bivalent C_{1-6} non-cyclic hydrocarbon groups, $-(CH_2)_{w3}CONH(CH_2)_{w4}-$, $-(CH_2)_{w3}COO(CH_2)_{w4}-$ (symbols have the same meaning as defined above); more preferably C_{1-3} alkylene (e.g. $-CH_2-$, $-(CH_2)_2-$,
15 $-(CH_2)_3-$, etc.), $-(CH_2)_{w3}CONH(CH_2)_{w4}-$, $-(CH_2)_{w3}COO(CH_2)_{w4}-$ (symbols have the same meaning as defined above); especially preferably C_{1-3} alkylene (e.g. $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, etc.), etc.

20 As "substituents" and "monocyclic aromatic rings" in "monocyclic aromatic rings which may be condensed with 4 to 8 membered non-aromatic rings, and may have further substituents" for Ar, those exemplified as "substituents" and "cyclic group" in the "cyclic group which may have
25 substituents" for the above Ar^1 can be used. The number of substituents is, for instance, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

The substituents are preferably formyl, optionally
30 halogenated C_{1-6} alkyl-carbonyl, optionally halogenated C_{1-6} alkylsulfonyl, etc.

Here, as "optionally halogenated C_{1-6} alkyl-carbonyl" and "optionally halogenated C_{1-6} alkylsulfonyl", those exemplified as "substituents" in " C_{7-19} aralkyl which may
35 have substituents" can be used respectively.

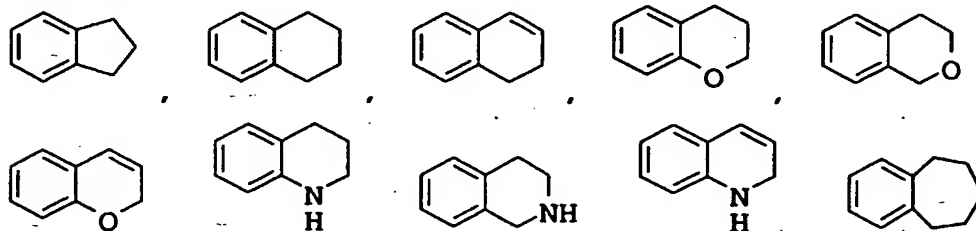
Examples of "4 to 8 membered non-aromatic rings" in the "monocyclic aromatic rings which may be condensed with 4 to 8 membered non-aromatic rings, and may have further substituents" include C₄₋₈ monocyclic non-aromatic hydrocarbon rings, 4 to 8 membered monocyclic non-aromatic hetero rings.

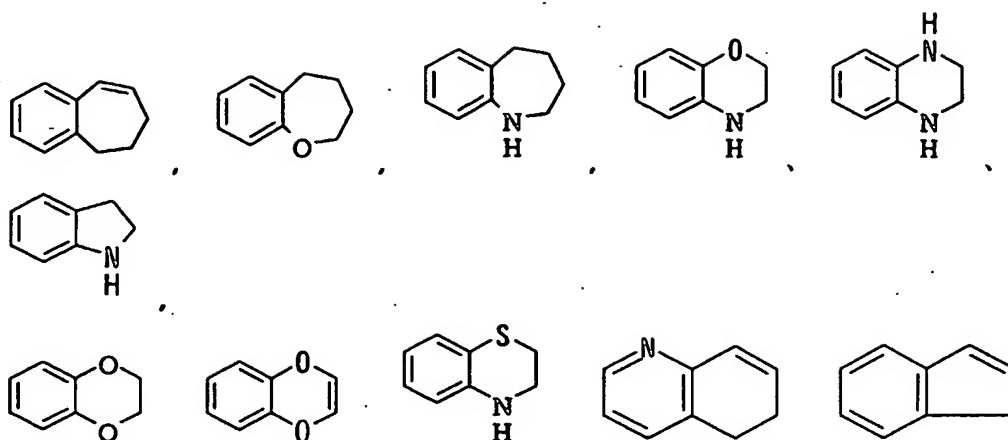
Examples of the "C₄₋₈ monocyclic non-aromatic hydrocarbon rings" include C₄₋₈ cycloalkane and C₄₋₈ cycloalkene. Concrete examples include cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, cyclopentene, cyclohexene, cycloheptene. Especially, cyclopentane, cyclohexane, cyclobutane, etc. are preferable.

Examples of the "4 to 8 membered monocyclic non-aromatic hetero rings" include azetidene, pyrrolidine, pyrroline, pyrazolidine, 2- or 3-pyrazoline, imidazoline, piperidine, piperazine, azepine, azokane, oxane, oxine, oxepane, oxazolidine, 2-oxazoline, thiazolidine, 2-thioazoline, morpholine, thiomorpholine.

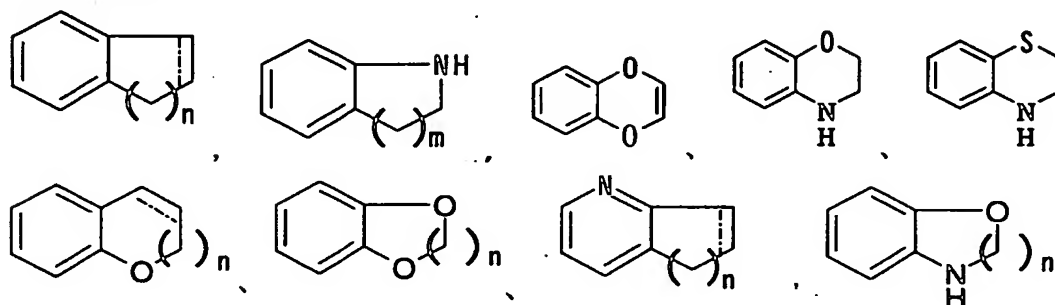
The above "4 to 8 membered non-aromatic rings" may have 1 to 3 substituents at a substitutable position. Examples of such substituents include optionally halogenated C₁₋₆ alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.), cyano, hydroxy.

Regarding Ar, concrete examples of "monocyclic aromatic rings which may be condensed with 4 to 8 membered non-aromatic rings, and may have further substituents" include



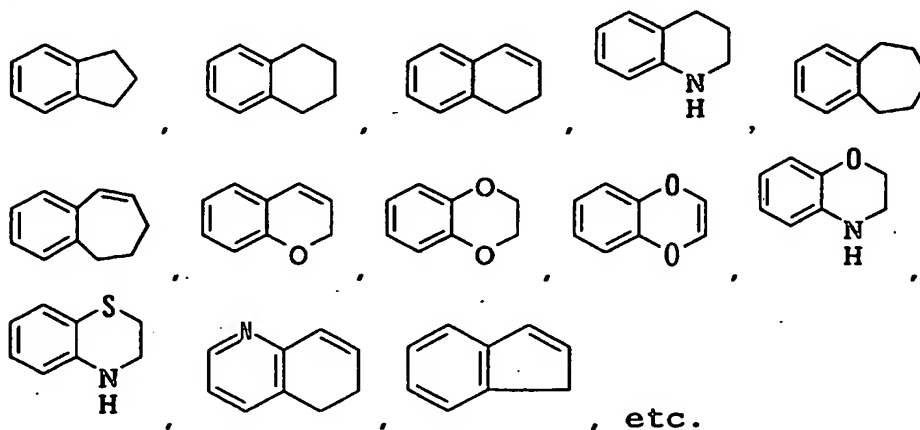


Ar is preferably benzene, pyridine, or rings of the
5 formulae :



wherein ----- is a single bond or double bond; each of m
and n is an integer of 1 to 4.

10 Ar is more preferably benzene, pyridine, rings of the
formulae :



, etc.

15 As the "hydrocarbon groups which may have
substituents" for R¹ and R², those exemplified as the above R³

can be used.

The "hydrocarbon groups which may have substituents" are preferably "C₁₋₆ alkyl which may have substituents".

Here, examples of "C₁₋₆ alkyl" in the "C₁₋₆ alkyl which may have substituents" include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl. Especially, methyl, ethyl, propyl, etc. are preferable.

Examples of "substituents" in the "C₁₋₆ alkyl which may have substituents" include halogen atom (e.g. fluorine, chlorine, bromine, iodine, etc.), C₁₋₃ alkylenedioxy (e.g. methylenedioxy, ethylenedioxy etc.), nitro, cyano, optionally halogenated C₃₋₆ cycloalkyl, optionally halogenated C₁₋₆ alkoxy, optionally halogenated C₁₋₆ alkylthio, hydroxy, amino, mono-C₁₋₆ alkylamino (e.g. methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), di-C₁₋₆ alkylamino (e.g. dimethylamino, diethylamino, dipropylamino, dibutylamino, ethylmethylamino, etc.), formyl, carboxy, carbamoyl, thiocarbamoyl, optionally halogenated C₁₋₆ alkyl-carbonyl, optionally halogenated C₁₋₆ alkoxy-carbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl, etc.), mono-C₁₋₆ alkyl-carbamoyl (e.g. methylcarbamoyl, ethylcarbamoyl, etc.), di-C₁₋₆ alkyl-carbamoyl (e.g. dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl etc.), optionally halogenated C₁₋₆ alkylsulfonyl, formylamino, optionally halogenated C₁₋₆ alkyl-carboxamide, C₁₋₆ alkoxy-carboxamide (e.g. methoxycarboxamide, ethoxycarboxamide, propoxycarboxamide, butoxycarboxamide, etc.), C₁₋₆ alkylsulfonylamino (e.g. methylsulfonylamino, ethylsulfonylamino, etc.), C₁₋₆ alkyl-carbonyloxy (e.g. acetoxy, propanoyloxy, etc.), C₁₋₆ alkoxy-carbonyloxy (e.g. methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, butoxycarbonyloxy, etc.), mono-C₁₋₆ alkyl-carbamoyloxy (e.g. methylcarbamoyloxy,

ethylcarbamoyloxy, etc.), di-C₁₋₆ alkyl-carbamoyloxy (e.g. dimethylcarbamoyloxy, diethylcarbamoyloxy, etc.), and aromatic groups which may have substituents. The number of substituents is, for instance, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

Here, as "optionally halogenated C₃₋₆ cycloalkyl," "optionally halogenated C₁₋₆ alkoxy" and "optionally halogenated C₁₋₆ alkylthio", those exemplified as "substituents" in the above "cyclic group which may have substituents" can be used.

As "optionally halogenated C₁₋₆ alkyl-carbonyl," "optionally halogenated C₁₋₆ alkylsulfonyl" and "optionally halogenated C₁₋₆ alkyl-carboxamide", those exemplified as "substituents" in the above "C₇₋₁₉ aralkyl which may have substituents" can be used.

As "substituents" and "aromatic groups" in the "aromatic groups which may have substituents", those exemplified as "substituents" and "aromatic groups" in the "cyclic group which may have substituents" for the above Ar¹ can be used. The number of substituents is, for instance, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

Examples of "nitrogen-containing hetero rings" in the "nitrogen-containing hetero rings which may have substituents" formed by R¹ and R² together with the adjacent nitrogen atom, include 3 to 8 membered nitrogen-containing hetero rings which contain at least one nitrogen atom in addition to carbon atoms, and which may further contain 1 to 3 hetero atoms selected from nitrogen, sulfur and oxygen atom. Concrete examples include aziridine, azetidine, morpholine, thiomorpholine, piperidine, piperazine, pyrrolidine, hexamethyleneimine, heptamethyleneimine, hexahydropyrimidine, 1,4-diazepan, 4,5-dihydro-imidazole, and their unsaturated cyclic amines (e.g.

1,2,5,6-tetrahydropyridine, etc.) can be mentioned. Especially, morpholine, piperidine, piperazine, pyrrolidine.

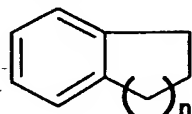
As "substituents" in the "nitrogen-containing hetero rings which may have substituents", for instance, those exemplified as "substituents" in the above "5 to 7 membered saturated cyclic amino which may have substituents" can be used. The number of substituents is, for instance, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

R^1 and R^2 are preferably C_{1-6} alkyl, more preferably methyl, ethyl, propyl, etc.

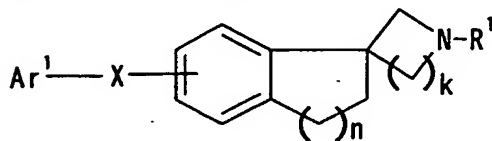
Also, it is preferable that R^1 and R^2 , together with the adjacent nitrogen atom, form piperidino, pyrrolidin-1-yl, piperazin-1-yl etc.

And, it is preferable that at least one of R^1 and R^2 is C_{1-6} alkyl which may have substituents. It is especially preferable that both R^1 and R^2 is C_{1-6} alkyls which may have substituents.

R^2 can form a spiro ring together with Ar. For instance, Ar is a ring of the formula :



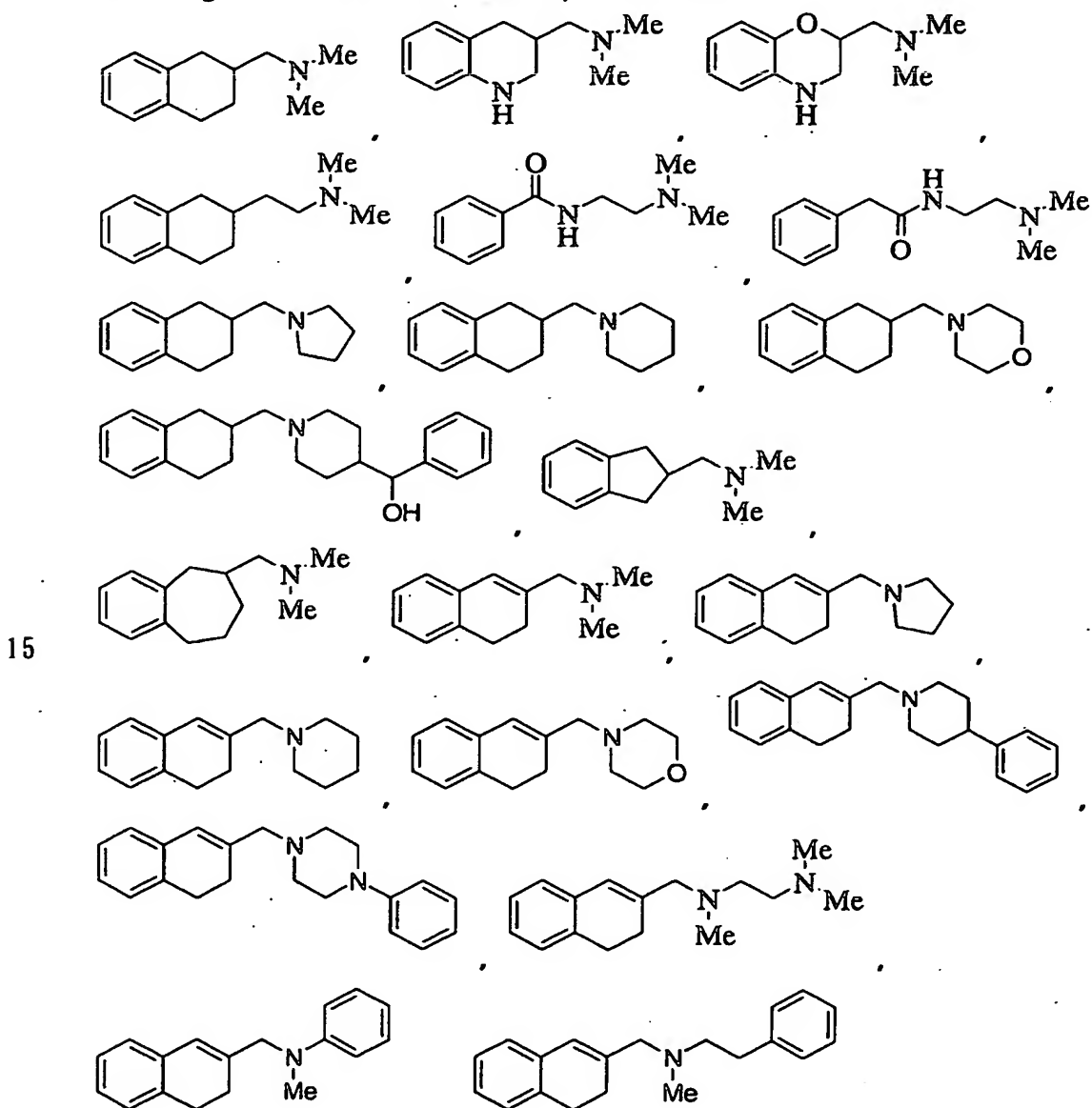
wherein n is an integer of 1 to 4; and Y is methylene; R^2 can form a spiro ring together with Ar. Examples of the spiro ring include



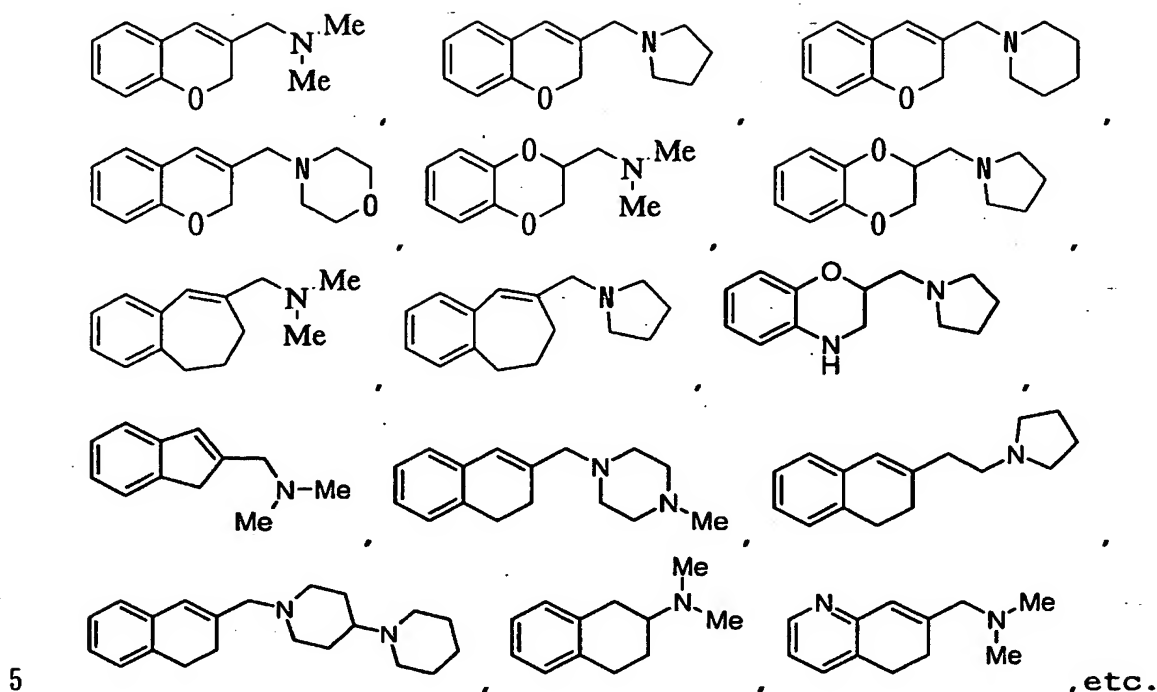
wherein k (ring Ar and N are connected by $-(CH_2)_k-$) is an integer of 1 to 4; and other symbols have the same meaning as defined above.

R^2 may form, together with the adjacent nitrogen atom and Y, a nitrogen-containing hetero ring which may have substituents. Examples of the "nitrogen-containing hetero ring which may have substituents" include those exemplified as the "nitrogen-containing hetero rings which may have substituents" formed by R^1 and R^2 together with the adjacent nitrogen atom.

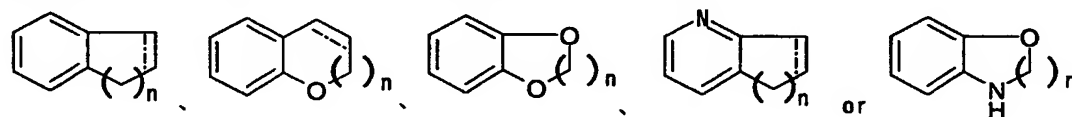
In formula (I), preferable examples of the partial structural formula : $Ar-Y-N(R^1)R^2$ (symbols have the same meanings as defined above) include



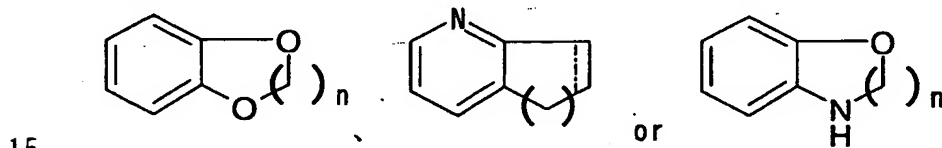
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Among the compounds of the formula (I), a compound wherein Ar is a ring of the formula :



10 wherein ----- is a single bond or double bond, n is an integer of 1 to 4, and each ring may have substituents;
 X is $-\text{CONR}^{\text{sc}}-$, $-\text{NR}^{\text{sc}}\text{CO}-$, $-\text{CH}=\text{CH}-\text{CONR}^{\text{sc}}-$ or $-\text{SO}_2\text{NR}^{\text{sc}}-$ where R^{sc} is hydrogen atom or C_{1-6} alkyl;
 Y is a spacer having a main chain of 1 to 6 atoms;
 provided that Ar is a ring of the formulae :



15 wherein symbols have the same meanings as defined above, and each ring may have substituents, when X is $-\text{SO}_2\text{NH}-$; and provided that Ar^1 is not biphenyl which may be substituted; when X is $-\text{CONH}-$ and Ar is any one of
 20 benzopyran, dihydrobenzopyran, dihydrobenzoxazine, dihydrobenzoxazole or tetrahydrobenzoxazepine;

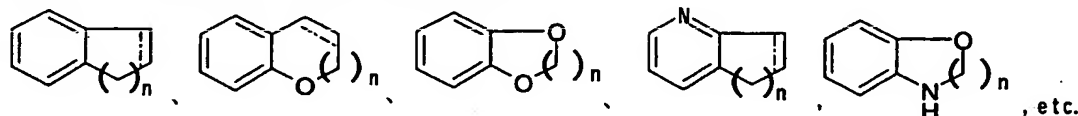
(excluding N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]-4-biphenylcarboxamide);

namely compound of the formula (I') (excluding N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]-4-

5 biphenylcarboxamide) is a novel compound.

Preferred examples of compound of the formula (I') include compound of the formula (I'-1), (I'-2), (I'-3), (I'-4), (I'-5), (I'-6), (I'-7), (I'-8), (I'-9) or (I'-10).

In the above formulae (I'), (I'-1), (I'-2), (I'-3),
10 (I'-4), (I'-5), (I'-6), (I'-7), (I'-8), (I'-9) and (I'-10), a ring of the formula :



wherein symbols have the same meanings as above,
may have further 1 to 3 substituents at substitutable
15 positions.

Examples of such substituents include "substituents" exemplified in the above Ar. Especially, preferred are formyl, optionally halogenated C₁₋₆ alkyl-carbonyl, optionally halogenated C₁₋₆ alkylsulfonyl, optionally
20 halogenated C₁₋₆ alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.), cyano, hydroxy, etc.

Examples of salts of compound (I) or (I') include salts
25 with inorganic bases, ammonium salts, salts with organic bases, salts with inorganic acids, salts with organic acids, and salts with basic or acidic amino acids.

Preferred examples of salts with inorganic bases include alkali metal salts such as sodium salts and
30 potassium salts; alkaline earth metal salts such as calcium salts, magnesium salts, barium salts; and aluminum salts.

Preferred examples of salts with organic bases include salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine,

dicyclohexylamine, N,N-dibenzylethylenediamine.

Preferred examples of salts with inorganic acids include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid.

5 Preferred examples of salts with organic acids include salts with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, and p-toluenesulfonic acid,
10 3-chlorobenzoic acid.

Preferred examples of salts with basic amino acids include salts with arginine, lysine, ornithine. Preferred examples of salts with acidic amino acids include salts with aspartic acid, glutamic.

15 Among these salts, pharmaceutically acceptable salts are preferable. For instance, when compound (I) or (I') possesses an acidic functional group, it can form an inorganic salt such as an alkali metal salt (e.g., sodium salt, potassium salt, etc.), an alkaline earth metal salt
20 (e.g. calcium salt, magnesium salt, barium salt, etc.), and an ammonium salt. When compound (I) or (I') possesses a basic functional group, it can form an inorganic salt such as hydrochloride, sulfate, phosphate, hydrobromate, etc.; or an organic salt such as acetate, maleate, fumarate,
25 succinate, methanesulfonate, p-toluenesulfonate, citrate and tartrate.

Compounds (I) and (I') (hereinafter also abbreviated as a compound of the invention) can be either anhydrides or hydrates. A hydrate may have 0.5 to 3 water molecules.

30 In addition, a compound of the invention can be labeled using isotopes (e.g. ^3H , ^{14}C , and ^{35}S , etc.).

When a compound of the invention contains optical isomers, stereoisomers, regio isomers, rotational isomers,
35 these are included as a compound of the invention, and each of them can be obtained as a single substance by per se known

synthesis methods and separation methods. For instance, when optical isomers exist in a compound of the invention, the optical isomers separated from the compound are included in a compound of the invention.

5 The optical isomers can be produced using per se known methods. Concretely, the optical isomer can be obtained by using an optically active synthetic intermediate, or subjecting the racemic mixture of the final product to optical resolution in accordance with common method.

10 Examples of optical resolution methods include per se known methods such as the fractional recrystallization method, chiral column method, diastereomer method, etc., which are described in detail below.

1) Fractional recrystallization method

15 The method which comprises allowing a racemate to form a salt with an optically active compound (e.g. (+)-mandelic acid, (-)-mandelic acid, (+)-tartaric acid, (-)-tartaric acid, (+)-1-phenethylamine, (-)-1-phenethylamine, cinchonine, (-)-cinchonidine, brucine, etc.), separating
20 the salt using a fractional recrystallization method, followed by, if desired, neutralizing process to obtain a free optical isomer.

2) Chiral column method

25 This method comprises subjecting a racemate or its salt to a column for separating an optical isomer (chiral column) for separation. For instance, in the case of liquid chromatography, an optical isomer mixture is added to the chiral column such as ENANTIO-OVM [produced by Tosol] or CHIRAL series [produced by Daicel], which is developed
30 using water, various buffer solutions (e.g. phosphate buffer), organic solvents (e.g. ethanol, methanol, isopropanol, acetonitrile, trifluoroacetic acid, diethylamine, etc.) as single or mixed solutions, and the optical isomers are separated. Also, in the case of gas
35 chromatography, for instance, separation is conducted using a chiral column such as CP-Chirasil-DeX (produced by

G.L.Science Co.).

3) Diastereomer method

In this method, a racemic mixture is subjected to a chemical reaction with an optically active reagent to give a diastereomer mixture, which is separated into a single substance by an ordinary separation means (e.g. fractional recrystallization, chromatography method, etc.). This single substance is subjected to removal of the optically active reagent part using chemical processing such as a hydrolysis reaction. For instance, when a compound of the invention possesses hydroxy or primary or secondary amino in its molecule, this compound is subjected to a condensation reaction with an optically active organic acid (e.g. MTPA [α -methoxy- α -(trifluoromethyl)phenylacetic acid], (-)-menthoxyacetic acid, etc.), to give the diastereomer in an ester form or an amide form, respectively. On the other hand, when a compound of the invention possesses carboxylic acid group, this compound is subjected to a condensation reaction with an optically active amine or alcohol reagent, to give the diastereomer in an amide form or an ester form, respectively. The separated diastereomer can be converted to an optical isomer of the original compound, by applying acidic hydrolysis or basic hydrolysis.

A prodrug of compound (I') is a compound which is converted to compound (I') by reactions involving enzymes and gastric acid, etc. under physiological conditions in the living body; in other words, a compound that is changed into compound (I') by enzymatically-caused oxidation, reduction and hydrolysis, and a compound that is changed into compound (I') by hydrolysis caused by gastric acid.

Examples of the prodrugs of compound (I') include compounds in which amino groups of compound (I') have been acylated, alkylated, or phosphorylated [e.g. compounds in which amino groups of compound (I') have been eicosanoylated, aranylated, pentylaminocarbonylated,

(5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylated, tetrahydrofuranylated, pyrrolidylmethylated, pivaloyloxymethylated, tert-butylated, etc.]; compounds in which hydroxyl groups of compound (I') have been
5 acylated, alkylated, phosphorylated, borated (e.g. compounds in which hydroxyl groups of compound (I') have been acetylated, palmitoylated, propanoylated, pivaloylated, succinylated, fumarilated, alanilated, dimethylaminomethylcarbonylated, etc.); compounds in
10 which carboxyl groups of compound (I') have been esterified or amidated [e.g. compounds in which carboxyl groups of compound (I') have been ethylesterified, phenylesterified, carboxylmethylesterified, dimethylaminomethylesterified,
15 pivaloyloxymethylesterified, ethoxycarbonyloxyethylesterified, phthalidylesterified, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methylesterified, cyclohexyloxycarbonylethylesterified, or methylamidated, etc.]. These compounds can be produced from compound (I')
20 using per se known methods.

Also, a prodrug of compound (I') can be a compound which is changed to compound (I') by physiological conditions, as described in pages 163 to 198 of Molecular Design, Volume 7, "Development of Drugs," published in
25 1990 by Hirokawa Shoten.

A compound of the invention can be produced in accordance with per se known methods such as methods described in WO9838156, WO9532967, and EP-A533266, etc.,
30 or analogous methods thereto.

For instance, a compound of the invention can be produced in accordance with [Production method 1] to [Production method 6] which are described in detail below, or analogous methods thereto.

35 Compounds (II) to (XI) used as raw materials, can be used in the form of salts. As such salts, those exemplified

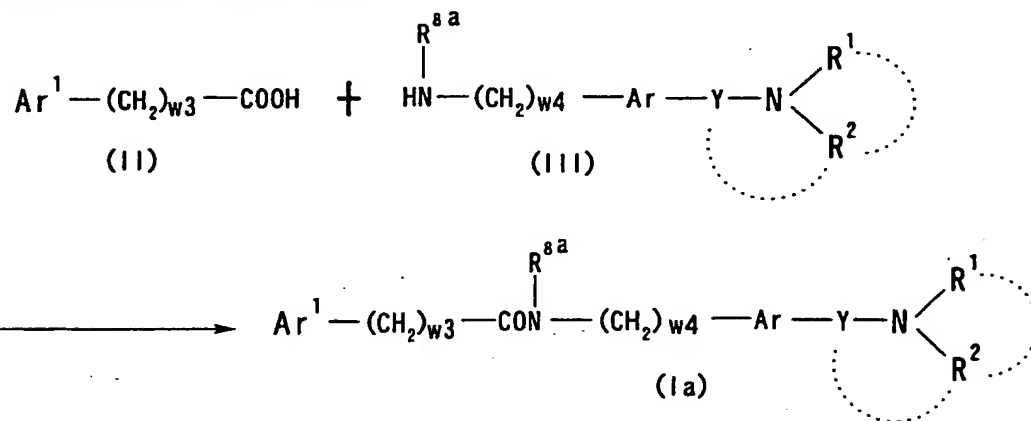
as salts of the above compound (I) or (I') can be used.

In the following [Production method 1] to [Production method 6], when an alkylation reaction, a hydrolysis reaction, an amination reaction, an esterification reaction, an amidation reaction, an esterification reaction, an etherification reaction, an oxidation reaction, a reduction reaction, etc. are carried out, these reactions are carried out in accordance with per se known methods. Examples of such methods include the methods described in Organic Functional Group Preparations, Second Edition, Academic Press, Inc., published in 1989; Comprehensive Organic Transformations, VCH Publishers Inc., published in 1989, etc.

[Production method 1]

Compound (Ia) having $-(CH_2)_{w3}CONR^{8a}(CH_2)_{w4}-$ for X in formula (I), is produced, for instance, by the following amidation reaction.

(Amidation reaction)



wherein R^{8a} is hydrogen atom or an optionally halogenated C_{1-6} alkyl; other symbols have the same meanings as defined above.

As the "optionally halogenated C_{1-6} alkyl", those exemplified as "substituents" in the above "cyclic group which may have substituents" can be used.

The "amidation reaction" includes the following

"method using a dehydration and condensation agent" and
"method using a reactive derivative of carboxylic acid".

i) Method using a dehydration and condensation agent

5 Compound (III), 1 to 5 equivalents of compound (II),
and 1 to 2 equivalents of a dehydration and condensation
agent are reacted in an inert solvent. If necessary, the
reaction can be carried out with the coexistence of 1 to
1.5 equivalents of 1-hydroxybenzotriazole (HOBT) and (or)
10 catalytic quantity to 5 equivalents of a base.

Examples of the "dehydrating and condensation agent"
include dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-
dimethylaminopropyl)carbodiimide hydrochloride (WSC).
WSC is particularly preferable.

15 Examples of the "inert solvent" include nitrile
solvents (preferably acetonitrile), amide solvents
(preferably DMF), halogenated hydrocarbon solvents
(preferably dichloromethane), ether solvents (preferably
THF). Two or more kinds of these can be mixed in an
20 appropriate ratio for use.

Examples of the "base" include

1) for instance, strong bases such as hydrides of
alkali metals or alkaline earth metals (e.g. lithium
25 hydride, sodium hydride, potassium hydride, calcium
hydride, etc.), amides of alkali metals or alkaline earth
metals (e.g. lithium amide, sodium amide, lithium
diisopropylamide, lithium dicyclohexylamide, lithium
hexamethyldisilazide, sodium hexamethyldisilazide,
30 potassium hexamethyldisilazide, etc.), lower alkoxides of
alkali metals or alkaline earth metals (e.g. sodium
methoxide, sodium ethoxide, potassium tert-butoxide,
etc.);

2) for instance, inorganic bases such as hydroxides
35 of alkali metals or alkaline earth metals (e.g. sodium
hydroxide, potassium hydroxide, lithium hydroxide, barium

hydroxide, etc.), carbonates of alkali metals or alkaline earth metals (e.g. sodium carbonate, potassium carbonate, cesium carbonate, etc.) and hydrogencarbonates of alkali metals or alkaline earth metals (e.g. sodium hydrogencarbonate, potassium hydrogencarbonate, etc.);
5 and

3) for instance, amines such as triethylamine, diisopropylethylamine, N-methylmorpholine, dimethylaminopyridine, DBU (1,8-
10 diazabicyclo[5.4.0]undec-7-en), DBN (1,5-diazabicyclo[4.3.0]non-5-en); for instance, organic bases such as basic heterocyclic compounds of pyridine, imidazole, 2,6-lutidine, etc.

Among the above bases, triethylamine, 4-
15 dimethylaminopyridine, etc., are preferable.

Reaction temperature is usually room temperature (0°C to 30°C, hereafter the same). Reaction time is, for instance, 10 to 24 hours.

ii) Method using a reactive derivative of carboxylic acid
20 A reactive derivative of compound (II) and 1 to 5 equivalents (preferably 1 to 3 equivalents) of compound (III) are reacted in an inert solvent. If necessary, the reaction can be carried out with the coexistence of 1 to 10 equivalents, preferably 1 to 3 equivalents of a base.

25 Examples of the "reactive derivative" of compound (II) include acid halides (e.g., acid chloride, acid bromide, etc.), mixed acid anhydrides (e.g. acid anhydrides with C₁₋₆ alkyl-carboxylic acid, C₆₋₁₀ aryl-carboxylic acid or C₁₋₆ alkylcarbonate), active esters (e.g. esters with phenol
30 which may have substituents, 1-hydroxybenzotriazole or N-hydroxysuccinimide, etc.).

Examples of the "substituents" in the "phenol which may have substituents" include halogen atom (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, optionally
35 halogenated C₁₋₆ alkyl, optionally halogenated C₁₋₆ alkoxy. The number of substituents is, for instance, 1 to 5.

As the "optionally halogenated C₁₋₆ alkyl" and "optionally halogenated C₁₋₆ alkoxy", those exemplified as "substituents" in the above "cyclic group which may have substituents" can be used.

5 Concrete examples of "phenol which may have substituents" include phenol, pentachlorophenol, pentafluorophenol, p-nitrophenol. The reactive derivative is, preferably, an acid halide.

10 Examples of the "inert solvent" include ether solvents, halogenated hydrocarbon solvents, aromatic solvents, nitrile solvents, amide solvents, ketone solvents, sulfoxide solvents, and water. Two or more kinds of these can be mixed in an appropriate ratio for use.

Especially, acetonitrile, THF, dichloromethane, 15 chloroform, etc. are preferable.

As the "base", the same as above are used. The base is preferably sodium hydride, potassium carbonate, sodium carbonate, sodium hydroxide, potassium hydroxide, sodium hydrogencarbonate, potassium hydrogencarbonate, 20 triethylamine, pyridine, etc.

Reaction temperature is usually -20°C to 50°C, preferably room temperature. Reaction time is usually 5 minutes to 40 hours, preferably 1 to 18 hours.

Compound (III) can be produced by per se known methods.

25 For instance, 6-amino-2-(N,N-dimethylamino)methyltetraline or its salt can be produced in accordance with the methods described in WO9838156.

Also, 6-amino-2,3-dihydro-1-(2-dimethylaminoethyl)-1H-indole, 6-amino-3,4-dihydro-4-(2-dimethylaminoethyl)- 30 2H-1,4-benzoxazine, etc., can be produced in accordance with the methods described in WO9532967.

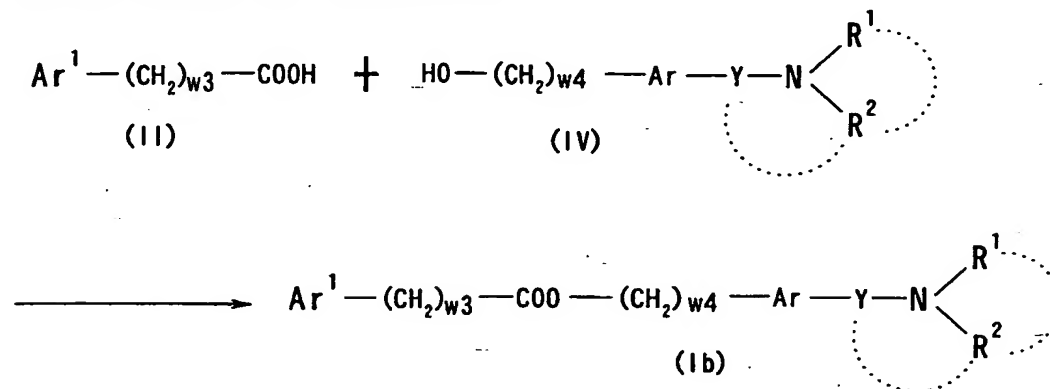
The above "method using a reactive derivative of carboxylic acid" can be also adopted when producing a corresponding sulfonamide derivative or sulfinamide 35 derivative, from the sulfonic acid of the formula :
 $\text{Ar}^1-(\text{CH}_2)_{w3}-\text{SO}_2\text{OH}$ (symbols have the same meanings as defined

above), or the sulfinic acid of the formula : $\text{Ar}^1-(\text{CH}_2)_{w3}-\text{SOOH}$ (symbols have the same meanings as defined above).

[Production method 2]

5 Compound (Ib) having $-(\text{CH}_2)_{w3}-\text{COO}(\text{CH}_2)_{w4}-$ for X in the formula (I), can be produced by the following esterification reaction.

(Esterification reaction)



10 wherein symbols have the same meanings as defined above.

A reactive derivative of compound (II) and 1 to 5 equivalents (preferably 1 to 3 equivalents) of compound (IV) is reacted in an inert solvent. Usually, this reaction is carried out with the coexistence of 1 to 10 equivalents, preferably 1 to 3 equivalents of a base.

As the reactive derivative of compound (II), the same as above is used. Especially, an acid halide is preferable.

20 Examples of the "inert solvent" include ether solvents, halogenated hydrocarbon solvents, aromatic solvents, nitrile solvents, amide solvents, ketone solvents, sulfoxide solvents. Two or more kinds of these can be mixed in an appropriate ratio for use. Especially, acetonitrile, dichloromethane, chloroform, etc. are preferable.

25 As the "base", the same one as above can be used. The base is preferably sodium hydride, potassium carbonate, sodium carbonate, sodium hydroxide, potassium hydroxide, sodium hydrogencarbonate, potassium hydrogencarbonate,

triethylamine, pyridine, etc.

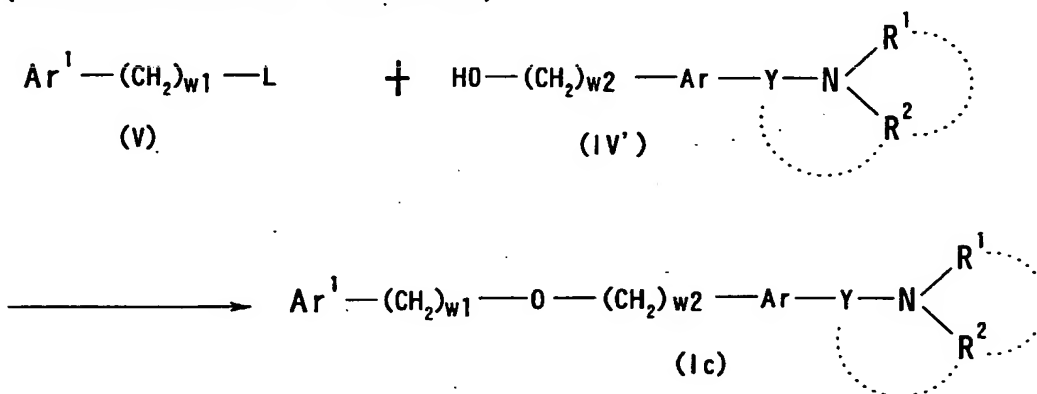
Reaction temperature is usually -20°C to 50°C , preferably room temperature. Reaction time is usually 5 minutes to 40 hours, preferably 1 to 18 hours.

5

[Production method 3]

Compound (Ic) having $-(\text{CH}_2)_{w1}\text{O}(\text{CH}_2)_{w2}-$ for Y in the formula (I), can be produced by, for instance, the following etherification reaction.

10 (Etherification reaction)



wherein L is a leaving group, and other symbols have the same meanings as defined above.

15 Examples of the "leaving group" for L include halogen atom (e.g. chlorine, bromine, iodine, etc.), optionally halogenated C_{1-6} alkylsulfonyloxy (e.g. methanesulfonyloxy, ethanesulfonyloxy, trifluoromethanesulfonyloxy, etc.), C_{6-10} arylsulfonyloxy which may have substituents, hydroxy.

20 Examples of the "substituents" in the " C_{6-10} arylsulfonyloxy which may have substituents" include halogen atom (e.g. chlorine, bromine, iodine, etc.), optionally halogenated C_{1-6} alkyl, C_{1-6} alkoxy. The number of substituents is, for instance, 1 to 3. Concrete examples
25 of the C_{6-10} arylsulfonyloxy which may have substituents" include benzenesulfonyloxy, p-toluenesulfonyloxy, 1-naphthalenesulfonyloxy, 2-naphthalenesulfonyloxy.

The "leaving group" is preferably halogen atom (e.g.

chlorine, bromine, iodine, etc.), methanesulfonyloxy, trifluoromethanesulfonyloxy, p-toluenesulfonyloxy.

Compound (IV') and about 1 to 5 equivalents
5 (preferably 1 to 2 equivalents) of compound (V) are reacted in inert solvent, with the coexistence of base.

As the "base", the same one as above can be used. The base is preferably potassium carbonate, sodium hydrogencarbonate, triethylamine, N-methylmorpholine,
10 pyridine, etc. The amount of the base used is usually about 1 to 5 equivalents relative to compound (V).

Examples of the "inert solvent" include alcohol solvents, ether solvents, halogenated hydrocarbon solvents, aromatic solvents, nitrile solvents, amide
15 solvents, ketone solvents, sulfoxide solvents, water. Two or more kinds of these can be mixed in an appropriate ratio for use. Especially, acetonitrile, N,N-dimethylformamide (DMF), acetone, ethanol, pyridine, etc., are preferable.

Reaction temperature is about -20°C to 100°C,
20 preferably room temperature to 80°C. Reaction time is, for instance, 5 hours to 1 day.

In the above production method, when the leaving group is hydroxy, Mitsunobu reaction can usually be used. In the Mitsunobu reaction, compound (V) and 0.5 to 5 equivalents
25 (preferably 1 to 1.5 equivalents) of compound (IV') are reacted in inert solvent with the coexistence of 0.5 to 5 equivalents (preferably 1 to 1.5 equivalents) of ethyl acetyldicarboxylate.

Examples of the inert solvent include ether solvents,
30 halogenated hydrocarbon solvents, aromatic solvents, nitrile solvents, amide solvents, ketone solvents, sulfoxide solvents. Two or more kinds of these can be mixed in an appropriate ratio for use. Especially, acetonitrile, dichloromethane, chloroform, etc. are
35 preferable.

Reaction temperature is usually -20°C to 50°C,

preferably room temperature. Reaction time is usually 5 minutes to 40 hours, preferably 1 to 18 hours.

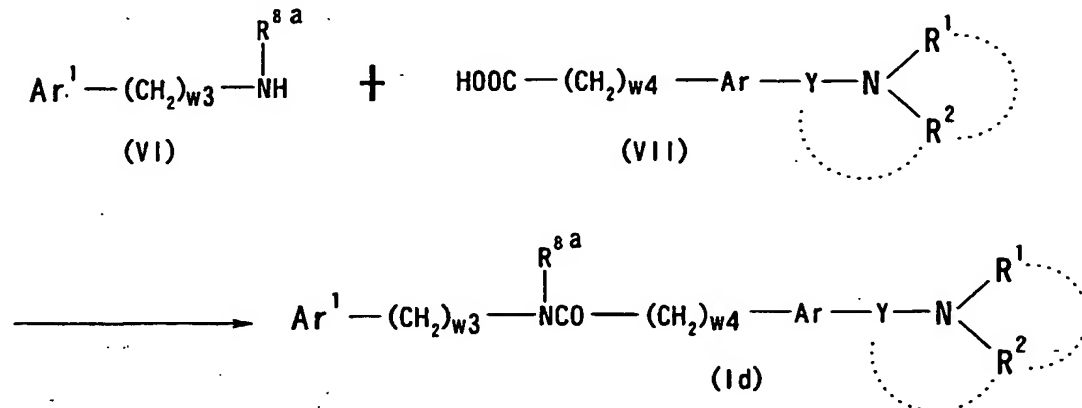
Compound (IV') can be produced by per se known methods.

For instance, 3-(N,N-dimethylamino)methyl-1,2,3,4-tetrahydro-7-quinolinol, 2-(N,N-dimethylamino)methyl-6-hydroxytetralin, 6-hydroxy-2-piperidinomethyltetralin, 2-[2-(N,N-dimethylamino)ethyl]-6-hydroxytetralin, 2-(N,N-dimethylamino)methyl-7-hydroxytetralin, 6-hydroxy-2-(N-methylamino)methyltetralin, etc., can be produced in accordance with the methods described in WO9838156.

[Production method 4]

Compound (Id) having $-(CH_2)_{w3}NR^{8a}CO(CN_2)_{w4}-$ for X in the formula (I), can be produced, for instance, by the following amidation reaction.

(Amidation reaction)



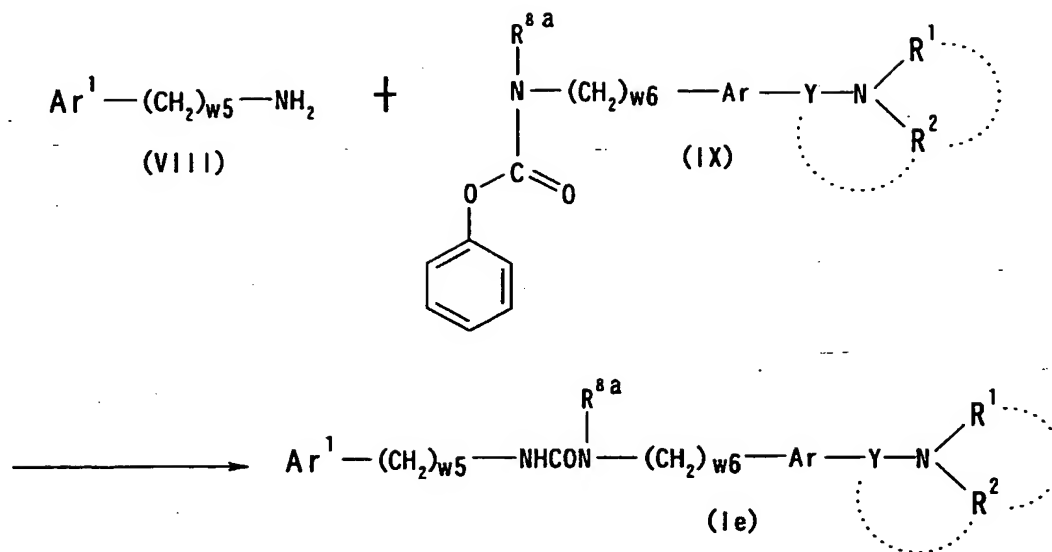
wherein symbols have the same meanings as defined above.

This Production method is carried out in accordance with the above Production method 1.

[Production method 5]

Compound (Ie) having $-(CH_2)_{w5}NHCONR^{8a}(CN_2)_{w6}-$ for X in the formula (I), can be produced, for instance, by the following urea reaction.

(Urea reaction)



wherein symbols have the same meanings as defined above.

Compound (IX) and 1 to 5 equivalents (preferably 1 to 1.5 equivalents) of compound (VIII) is reacted in an inert solvent with the coexistence of a base.

As the "base", the same one as above can be used. The base is preferably potassium carbonate, sodium carbonate, sodium hydroxide, potassium hydroxide, sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine, pyridine, etc.

Examples of the "inert solvent" include alcohol solvents, ether solvents, halogenated hydrocarbon solvents, aromatic solvents, nitrile solvents, amide solvents, ketone solvents, sulfoxide solvents, water. Two or more kinds of these can be mixed in an appropriate ratio for use. Especially, acetonitrile, DMF, acetone, ethanol, pyridine, etc. are preferable.

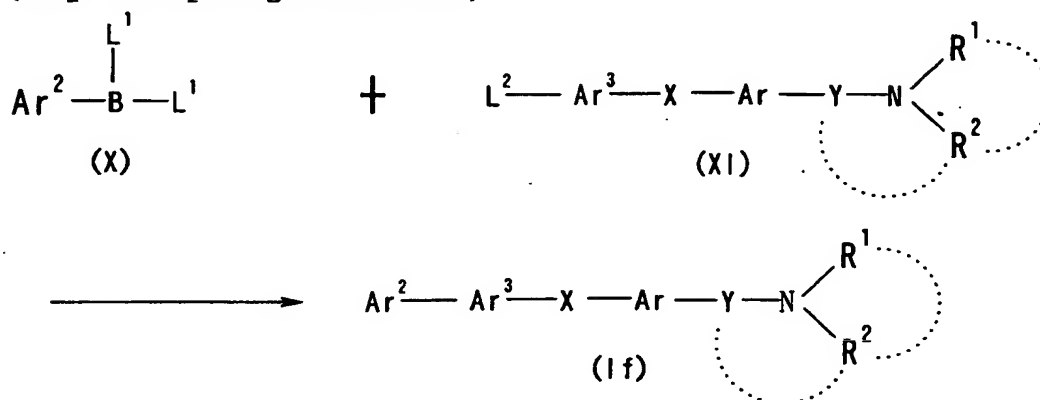
Reaction temperature is usually -20°C to 100°C , preferably room temperature to 80°C . Reaction time is, for instance, 0.5 hour to 1 day.

[Production method 6]

Compound (If) having, for Ar^1 , a ring assembly aromatic

group ($\text{Ar}^2\text{-Ar}^3$) which may have substituents in the formula (I), can be produced by, for instance, the following aryl-coupling reaction.

(Aryl-coupling reaction)



5 wherein Ar^2 and Ar^3 are monocyclic aromatic groups or condensed aromatic groups, each of which may have substituents; L^1 is hydroxy or C_{1-6} alkyl; L^2 is halogen (preferably chlorine, bromine) or
 10 trifluoromethanesulfonyloxy; other symbols have the same meanings as defined above.

As "substituents", "monocyclic aromatic groups" and "condensed aromatic groups" in the "monocyclic aromatic
 15 groups or condensed aromatic groups, each of which may have substituents" for Ar^2 and Ar^3 , those exemplified as the above Ar^1 can be used. Especially, it is preferable that both of Ar^2 and Ar^3 are phenyl groups which may have substituents, and $\text{Ar}^2\text{-Ar}^3$ is biphenyl which may have substituents.

20 The aryl-coupling reaction can be carried out in accordance with per se known methods such as the method described in Acta. Chemica Scandinavia, pp. 221-230, 1993, or methods analogous thereto.

Compound (X) and 1 to 3 equivalents (preferably 1 to
 25 1.5 equivalents) of compound (XI) are reacted in an inert solvent in the presence of a base and a transition metal catalyst.

As the base, the same one as above can be used. The

base is preferably sodium carbonate, sodium hydrogencarbonate, etc.

The amount of the "base" used is, for instance, about 1 to 10 equivalents relative to compound (XI).

5 Examples of the "transition metal catalyst" include palladium catalyst, nickel catalyst. Examples of the "palladium catalyst" include tetrakis(triphenylphosphine)palladium (O), palladium acetate, bis (triphenylphosphine) palladium (II) chloride, 10 palladium-carbon. Examples of the "nickel catalyst" include tetrakis(triphenylphosphine) nickel (O).

The amount of the "transition metal catalyst" used is about 0.01 to 1 equivalent, preferably about 0.01 to 0.5 equivalent, relative to compound (XI).

15 Reaction temperature is room temperature to 150°C, preferably about 80°C to 150°C. Reaction time is, for instance, about 1 to 48 hours.

Examples of the "inert solvent" include water, alcohol solvents, aromatic solvents. Two or more kinds of these 20 can be mixed in an appropriate ratio for use. Especially, a single solvent such as water, ethanol and toluene; or a mixed solvent of two or more kinds of these is preferable.

Examples of the above "alcohol solvents" include methanol, ethanol, isopropanol, tert-butanol.

25 Examples of the above "ether solvents" include diethylether, tetrahydrofuran (THF), 1,4-dioxane, 1,2-dimethoxyethane.

Examples of the above "halogenated hydrocarbon solvents" include dichloromethane, chloroform, 1,2- 30 dichloroethane, carbon tetrachloride.

Examples of the above "aromatic solvents" include benzene, toluene, xylene, pyridine.

Examples of the above "hydrocarbon solvents" include hexane, pentane, cyclohexane.

35 Examples of the above "amide solvents" include N,N-dimethylformamide (DMF), N,N-dimethylacetamide, N-

methylpyrrolidone.

Examples of the above "ketone solventd" include acetone, methylethylketone.

5 Examples of the above "sulfoxide solvents" include dimethylsulfoxide (DMSO).

Examples of the above "nitrile solvents" include acetonitrile, propionitrile.

10 In a compound of the invention thus obtained, the intramolecular functional group can be converted to a desired functional group by combining per se known chemical reactions. Examples of the chemical reactions include oxidation reaction, reduction reaction, alkylation reaction, hydrolysis reaction, amination reaction, esterification reaction, aryl-coupling reaction,
15 deprotection reaction.

In each of the above reactions, when the raw material compounds possess amino, carboxy, hydroxy, and/or carbonyl as substituents, protecting groups which are generally used in peptide chemicals, etc., can be introduced into these
20 groups, and the desired compound can be obtained by removing the protecting groups after the reaction if necessary.

Examples of the protecting group for amino include formyl, C₁₋₆ alkyl-carbonyl (e.g. acetyl, propionyl, etc.), C₁₋₆ alkoxy-carbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, etc.), benzoyl, C₇₋₁₀ aralkyl-carbonyl (e.g. benzylcarbonyl, etc.), C₇₋₁₄ aralkyloxy-carbonyl (e.g. benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl, etc.), trityl, phthaloyl, N,N-dimethylaminomethylene, silyl (e.g. trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyl-
25 dimethylsilyl, tert-butyl-diethylsilyl, etc.), C₂₋₆ alkenyl (e.g. 1-allyl, etc.). These groups may be substituted by 1 to 3 of halogen atom (e.g. fluorine, chlorine, bromine, iodine, etc.), C₁₋₆ alkoxy (e.g. methoxy, ethoxy, propoxy, etc.) or nitro, etc.
30

Examples of the protecting group for carboxy include

C₁₋₆ alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, etc.), C₇₋₁₁ aralkyl (e.g. benzyl, etc.), phenyl, trityl, silyl (e.g. trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyl

5 butyldiethylsilyl, etc.), C₂₋₆ alkenyl (e.g. 1-allyl, etc.). These groups may be substituted by 1 to 3 of halogen atom (e.g. fluorine, chlorine, bromine, iodine, etc.), C₁₋₆ alkoxy (e.g. methoxy, ethoxy, propoxy, etc.) or nitro.

Examples of the protective group for hydroxy include

10 C₁₋₆ alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, etc.), phenyl, trityl, C₇₋₁₀ aralkyl (e.g. benzyl, etc.), formyl, C₁₋₆ alkyl-carbonyl (e.g. acetyl, propionyl, etc.), benzoyl, C₇₋₁₀ aralkyl-carbonyl (e.g. benzylcarbonyl, etc.), 2-tetrahydropyranyl, 2-

15 tetrahydrofuranyl, silyl (e.g. trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyl

20 butyldiethylsilyl, etc.), C₂₋₆ alkenyl (e.g. 1-allyl, etc.). These groups may be substituted by 1 to 3 of halogen atom (e.g. fluorine, chlorine, bromine, iodine, etc.), C₁₋₆ alkyl (e.g. methyl, ethyl, n-propyl, etc.), C₁₋₆ alkoxy (e.g. methoxy, ethoxy, propoxy, etc.) or nitro, etc. can be substituted for these groups.

Examples of the protecting group for carbonyl include

25 cyclic acetal (e.g. 1,3-dioxane, etc.), and non-cyclic acetal (e.g. di-C₁₋₆ alkylacetal, etc.).

Removal of the above protecting groups can be carried out in accordance with per se known methods such as those described in Protective Groups in Organic Synthesis,

30 published by John Wiley and Sons (1980). For instance, the methods using acid, base, ultraviolet light, hydrazine, phenylhydrazine, sodium N-methyldithiocarbamate, tetrabutylammonium fluoride, palladium acetate, trialkylsilyl halide (e.g. trimethylsilyl iodide,

35 trimethylsilyl bromide, etc.), and a reduction method, etc. can be used.

A compound of the invention can be isolated and purified by per se known methods such as solvent extraction, changing of liquid properties, transdissolution, crystallization, recrystallization, chromatography, etc.

5 It is also possible to isolate and purify the raw material compounds of a compound of the invention, or their salts using the same known methods as above, but they can also be used as raw materials in the next process as a reaction mixture without being isolated.

10

A compound of the invention possesses an excellent MCH receptor antagonistic action, therefore, it is useful as an agent for preventing or treating diseases caused by MCH.

Also, a compound of the invention is low in toxicity, and
15 is excellent in oral absorbency and intracerebral transitivity.

Therefore, a melanin-concentrating hormone antagonist (hereafter, also abbreviated as "MCH antagonist") comprising a compound of the invention can be
20 safely administered to mammals (e.g. rats, mice, guinea pigs, rabbits, sheep, horses, swine, cattle, monkeys, humans, etc.) as an agent for preventing or treating diseases caused by MCH.

Here, examples of the diseases caused by MCH include
25 obesity (e.g. malignant mastocytosis, exogenous obesity, hyperinsular obesity, hyperplasmic obesity, hypophyseal adiposity, hypoplasmic obesity, hypothyroid obesity, hypothalamic obesity, symptomatic obesity, infantile obesity, upper body obesity, alimentary obesity,
30 hypogonadal obesity, systemic mastocytosis, simple obesity, central obesity, etc.), hyperphagia, emotional disorders, reproductive function disorders, memory disorders, dementia, hormonal disorders.

A compound of the invention is also useful as an agent
35 for preventing or treating lifestyle diseases such as diabetes, diabetic complications (e.g. diabetic

retinopathy, diabetic neuropathy, diabetic nephropathy, etc.), arteriosclerosis, and gonitis.

Further, a compound of the invention is useful as an anorectic agent.

5 A MCH antagonist and a pharmaceutical composition of the invention can be used in combination with an alimentary therapy (e.g., alimentary therapy for diabetes) and exercise.

10 A MCH antagonist and a pharmaceutical composition of the invention can be produced by subjecting compound (I) or compound (I') respectively, as it is, or together with a pharmacologically acceptable carrier, to pharmaceutical manufacturing process in accordance with a per se known means.

15 Here, examples of the pharmacologically acceptable carriers include various organic or inorganic carrier substances which are commonly used as materials for pharmaceutical preparations, such as excipients, lubricants, binders, and disintegrators in solid
20 preparations; solvents, solubilizing agents, suspending agents, isotonizing agents, buffering agents, soothing agents, in liquid preparations. Also, in the pharmaceutical manufacturing process, additives such as antiseptics, antioxidants, coloring agents, sweeteners,
25 absorbents, moistening agents, can be used, if necessary.

 Examples of the excipients include lactose, sucrose, D-mannitol, starch, cornstarch, crystalline cellulose, light anhydrous silicic acid.

30 Examples of the lubricants include magnesium stearate, calcium stearate, talc, colloidal silica.

 Examples of the binders include crystalline cellulose, sucrose, D-mannitol, dextrin, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, starch, saccharose, gelatin,
35 methylcellulose, carboxymethylcellulose sodium.

 Examples of the disintegrators include starch,

carboxymethylcellulose, carboxymethylcellulose calcium, crosscarmellose sodium, carboxymethylstarch sodium, low-substituted hydroxypropylcellulose (L-HPC).

5 Examples of the solvents include distilled water for injection, alcohol, propylene glycol, macrogol, sesame oil, corn oil.

10 Examples of the solubilizing agents include polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate.

15 Examples of the suspending agents include surfactants such as stearyltriethanolamine, sodium lauryl sulfate, lauryl amino propionic acid, lecithin, benzalkonium chloride, benzethonium chloride, glyceryl monostearate; or hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethylcellulose sodium, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose.

20 Examples of the isotonizing agents include glucose, D-sorbitol, sodium chloride, glycerin, D-mannitol.

Examples of the buffering agents include buffer solutions of phosphate, acetate, carbonate and citrate.

Examples of the soothing agents include benzyl alcohol.

25 Examples of the antiseptics include paraoxybenzoates, chlorobutanol, benzyl alcohol, phenethylalcohol, dehydroacetic acid, and sorbic acid.

Examples of the antioxidants include sulfite, ascorbic acid.

30 A MCH antagonist and a pharmaceutical composition of the invention can be safely administered orally or parenterally (e.g. by local, rectal and intravenous administration) in various dosage forms, for instance, as oral drugs such as tablets (including sugar-coated tablets and film-coated tablets), powders, granules, capsules
35 (including soft capsules), solutions; and parenteral

preparations such as injections (e.g. subcutaneous injections, intravenous injections, intramuscular injections, intraperitoneal injections, etc.), external preparations (e.g. nasal preparations, percutaneous preparations, ointments, etc.), suppositories (e.g. rectal suppositories, vaginal suppositories, etc.), sustained-release preparations (e.g. sustained-release microcapsules, etc.), pellets, drip infusions, etc.

The content of compound (I) in a MCH antagonist of the invention and the content of compound (I') in a pharmaceutical composition of the invention are, for instance, about 0.1 to 100 weight percent of the MCH antagonist or whole pharmaceutical composition, respectively.

The dose of a MCH antagonist and a pharmaceutical composition of the invention can be appropriately selected depending on the subject of administration, route of administration, disease, etc.

For instance, the dose per day when a MCH antagonist or a pharmaceutical composition of the invention is orally administered to an adult obesity patient (body weight: about 60 kg), is about 0.1 to about 500 mg, preferably about 1 to about 100 mg, more preferably about 5 to about 100 mg, in terms of compound (I) or compound (I'), each of which is an active ingredient. These amounts can be divided into one to several doses per day for administration.

The MCH antagonist and pharmaceutical composition of the invention can be used in combination with other concomitant drugs which do not interfere with the MCH antagonist and pharmaceutical composition of the invention, for the purpose of "strengthening of therapeutic effect against obesity", "reduction of dose of MCH antagonist", etc. Examples of the concomitant drugs include a "agents for treating diabetes", "agents for treating diabetic complications", "agents for treating obesity other than MCH antagonists", "agents for treating

hypertension", "agents for treating hyperlipidemia (agents for treating arteriosclerosis)", "agents for treating arthritis", "antianxiety agents", "antidepressant". Two or more kinds of these concomitant drugs can be combined
5 in an appropriate ratio for use.

Examples of the above "agents for treating diabetes" include insulin sensitizers, insulin secretion enhancers, biguanides, insulins, α -glucosidase inhibitors, β 3
adrenaline receptor agonists.

10 Examples of the insulin sensitizers include pioglitazone or its salt (preferably hydrochloride), troglitazone, rosiglitazone or its salt (preferably maleate), JTT-501, GI-262570, MCC-555, YM-440, DRF-2593, BM-13-1258, KRP-297, R-119702.

15 Examples of the insulin secretion enhancers include sulfonylureas. Concrete examples of the sulfonylureas include tolbutamide, chlorpropamide, trazamide, acetohexamide, glyclopyramide and its ammonium salt, glibenclamide, gliclazide, glimepiride.

20 Other than the above, examples of insulin secretion enhancers include repaglinide, nateglinide, mitiglinide (KAD-1229), JTT-608.

Examples of biguanides include metformin, buformin, phenformin.

25 Examples of insulins include animal insulins extracted from bovine or porcine pancreas; semi-synthetic human insulin which is enzymatically synthesized from insulin extracted from porcine pancreas; human insulin synthesized by genetic engineering, using Escherichia Coli
30 and yeast. As insulin, also employed are insulin-zinc containing 0.45 to 0.9 (w/w)% of zinc; protamine-insulin-zinc produced from zinc chloride, protamine sulfate and insulin. In addition, insulin can be an insulin fragment or derivative (e.g. INS-1, etc.).

35 Insulin can also include various types such as ultra immediate action type, immediate action type, two-phase

type, intermediate type, prolonged action type, etc., and these can be selected depending on the pathological conditions of patients.

5 Examples of α -glucosidase inhibitors include acarbose, voglibose, miglitol, emiglitate.

Examples of β 3 adrenaline receptor agonists include AJ-9677, BMS-196085, SB-226552, AZ40140.

10 Other than the above, examples of the "agents for treating diabetes" include ergoset, pramlintide, leptin, BAY-27-9955.

Examples of the above "agents for treating diabetic complications" include aldose reductase inhibitors, glycation inhibitors, protein kinase C inhibitors.

15 Examples of aldose reductase inhibitors include torulestat; eparlestat; imirestat; zenarestat; SNK-860; zopolrestat; ARI-509; AS-3201.

Examples of glycation inhibitors include pimagedine.

Examples of protein kinase C inhibitors include NGF, LY-333531.

20 Other than the above, examples of "agents for treating diabetic complications" include alprostadil, thiapride hydrochloride, cilostazol, mexiletine hydrochloride, ethyl eicosapentate, memantine, pimagedline (ALT-711).

25 Examples of the above "agents for treating obesity other than MCH antagonists" include lipase inhibitors and anorectics.

Examples of lipase inhibitors include orlistat.

30 Examples of anorectics include mazindol, dexfenfluramine, fluoxetine, sibutramine, baiamine, (S)-sibutramine, SR-141716, NGD-95-1.

Other than the above, examples of "agents for treating obesity other than MCH antagonists" include lipstatin.

35 Examples of the above "agents for treating hypertension" include angiotensin converting enzyme inhibitors, calcium antagonists, potassium channel openers, angiotensin II antagonists.

Examples of angiotensin converting enzyme inhibitors include captopril, enalapril, alacepril, delapril (hydrochloride), lisinopril, imidapril, benazepril, cilazapril, temocapril, trandolapril, manidipine
5 (hydrochloride).

Examples of calcium antagonists include nifedipine, amlodipine, efonidipine, nicardipine.

Examples of potassium channel openers include levcromakalim, L-27152, AL0671, NIP-121.

10 Examples of angiotensin II antagonists include losartan, candesartan cilexetil, valsartan, irbesartan, CS-866, E4177.

Examples of the above "agents for treating hyperlipidemia (agents for treating arteriosclerosis)"
15 include HMG-CoA reductase inhibitors, fibrate compounds.

Examples of HMG-CoA reductase inhibitors include pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin, lipantil, cerivastatin, itavastatin, ZD-4522, or their salts (e.g. sodium salts, etc.).

20 Examples of fibrate compounds include bezafibrate, clinofibrate, clofibrate, simfibrate.

Examples of the above "agents for treating arthritis" include ibuprofen.

25 Examples of the above "antianxiety agents" include chlordiazepoxide, diazepam, oxazolam, medazepam, cloxazolam, bromazepam, lorazepam, alprazolam, fludiazepam.

30 Examples of the above "antidepressants" include fluoxetine, fluvoxamine, imipramine, paroxetine, sertraline.

The timing of administration of the above concomitant drugs is not limited. The MCH antagonist or pharmaceutical composition and the concomitant drugs can be administered to the subject simultaneously or at staggered times.

35 The dosages of the concomitant drugs can be determined in accordance with clinically used dosages, and can be

appropriately selected according to the subject of administration, route of administration, diseases and combinations of drugs, etc.

5 The administration forms for the concomitant drugs are not particularly limited as long as a MCH antagonist or a pharmaceutical composition are used in combination with a concomitant drugs at the time of administration. Examples of such administration forms includes 1) administration of a single preparation obtained by simultaneous preparation
10 of MCH antagonist or pharmaceutical composition together with concomitant drugs, 2) simultaneous administration of two kinds of preparations obtained by separate preparation of MCH antagonist or pharmaceutical composition, and concomitant drugs, through the same route of
15 administration, 3) staggered administration of two kinds of preparations obtained by separate preparation of MCH antagonist or pharmaceutical composition, and concomitant drugs, through the same route of administration, 4) simultaneous administration of two kinds of preparations
20 obtained by separate preparation of MCH antagonist or pharmaceutical composition, and concomitant drugs, through different routes of administration, 5) staggered administration of two kinds of preparations obtained by separate preparation of MCH antagonist or pharmaceutical
25 composition, and concomitant drugs, through different routes of administration (for instance, administration of MCH antagonist or pharmaceutical composition; and concomitant drugs in this order; or administration in reverse order).

30 The ratio of combination of MCH antagonist or pharmaceutical composition with concomitant drugs can be appropriately selected in accordance with the subject of administration, route of administration and diseases, etc.

35 This invention further relates to "a pharmaceutical comprising a melanin-concentrating hormone antagonist in

combination with at least one species selected from the group consisting of an agent for treating diabetes, an agent for treating hypertension and an agent for treating arteriosclerosis".

5 Here, the "melanin-concentrating hormone antagonist" is not especially limited as long as it is a compound having a melanin-concentrating hormone antagonistic action, and may be either of a peptide compound or a non-peptide compound.

10 As "an agent for treating diabetes", "an agent for treating hypertension" and "an agent for treating arteriosclerosis", those exemplified as the above concomitant drugs can be mentioned.

15 These drugs can be used in the same manner as in the above "combination of MCH antagonist of the invention with concomitant drugs".

20 The pharmaceutical provides excellent effects such as "strengthening of therapeutic effect against obesity", "reduction of dose of MCH antagonist", etc. as compared to single use of each drug.

BEST MODE FOR CARRYING OUT THE INVENTION

25 This invention will be explained further in detail by the following Reference Examples, Examples, Preparation Examples, and Experimental Examples. However, these do not limit this invention, and they can be changed within the scope that does not deviate from the scope of this invention.

30 In the following Reference Examples and Examples, "room temperature" means 0 to 30°C. Anhydrous magnesium sulfate or anhydrous sodium sulfate was used to dry the organic layer. "%" means percent by weight, unless otherwise specified.

35 Infrared absorption spectra were determined by the diffuse reflectance method, using fourier transform type infrared spectrophotometer.

FABMS (pos) is mass spectrum determined by the (+) method, in Fast Atom Bombardment Mass Spectrometry.

5 Other symbols used in the description have the following meanings.

	s	: singlet
	d	: doublet
	t	: triplet
	q	: quartet
10	m	: multiplet
	br	: broad
	J	: coupling constant
	Hz	: Hertz
	CDCl ₃	: heavy chloroform
15	DMSO-d ₆	: heavy dimethylsulfoxide
	THF	: tetrahydrofuran
	DMF	: N,N-dimethylformamide
	DMSO	: dimethylsulfoxide
	WSCD	: 1-ethyl-3-(3-dimethylaminopropyl)
20		carbodiimide
	WSC	: 1-ethyl-3-(3-dimethylaminopropyl)
		carbodiimide hydrochloride
	¹ H-NMR	: proton nuclear resonance
		(Free substances were usually measured in
25		CDCl ₃ .)
	IR	: infrared absorption spectrum
	Me	: methyl
	Et	: ethyl
	HOBt	: 1-hydroxy-1H-benzotriazole
30	IPE	: diisopropyl ether
	DMAP	: 4-dimethylaminopyridine

35 In this specification and drawings, when bases and amino acids are shown by codes, these codes are based on those by the IUPAC-IUB Commission on Biochemical

Nomenclature or common codes in the concerned fields.
Examples of these codes are shown below. Also, where some optical isomers of amino acids can exist, the L form is shown unless otherwise specified.

5	DNA	: deoxyribonucleic acid
	cDNA	: complementary deoxyribonucleic acid
	A	: adenine
	T	: thymine
	G	: guanine
10	C	: cytosine
	RNA	: ribonucleic acid
	mRNA	: messenger ribonucleic acid
	dATP	: deoxyadenosine triphosphate
	dTTP	: deoxythymidine triphosphate
15	dGTP	: deoxyguanosine triphosphate
	dCTP	: deoxycytidine triphosphate
	ATP	: adenosine triphosphate
	EDTA	: ethylenediamine tetraacetic acid
	SDS	: sodium dodecyl sulfate
20	EIA	: enzyme immunoassay
	Gly	: glycine
	Ala	: alanine
	Val	: valine
	Leu	: leucine
25	Ile	: isoleucine
	Ser	: serine
	Thr	: threonine
	Cys	: cysteine
	Met	: methionine
30	Glu	: glutamic acid
	Asp	: aspartic acid
	Lys	: lysine
	Arg	: arginine
	His	: histidine
35	Phe	: phenylalanine
	Tyr	: tyrosine

	Tro	: tryptophan
	Pro	: proline
	Asn	: asparagine
	Gln	: glutamine
5	pGlu	: pyroglutamine
	Me	: methyl group
	Et	: ethyl group
	Bu	: butyl group
	Ph	: phenyl group
10	TC	: thiazolidine-4(R)-carboxamide group

Substituents, protecting groups and reagents frequently used in this specification, are shown by the following symbols.

15	Tos	: p-toluenesulfonyl
	CHO	: formyl
	Bzl	: benzyl
	Cl ₂ Bzl	: 2,6-dichlorobenzyl
	Bom	: benzyloxymethyl
20	Z	: benzyloxycarbonyl
	Cl-Z	: 2-chlorobenzyloxycarbonyl
	Br-Z	: 2-bromobenzyloxycarbonyl
	Boc	: t-butoxycarbonyl
	DNP	: dinitrophenol
25	Trt	: trityl
	Bom	: t-butoxymethyl
	Fmoc	: N-9-fluorenylmethoxycarbonyl
	HOBt	: 1-hydroxybenzotriazole
	HOObt	: 3,4-dihydro-3-hydroxy-4-oxo-1,2,3-
30		benzotriazine
	HONB	: 1-hydroxy-5-norbornene-2,3-
		dicarbodiimide
	DCC	: N,N'-dicyclohexylcarbodiimide

35 SEQ ID NO in the SEQUENCE LISTING in the specification of the present application shows the following sequences.

[SEQ ID NO : 1] shows a synthetic DNA used for screening of cDNA coding rat SLC-1.

5 [SEQ ID NO : 2] shows a synthetic DNA used for screening of cDNA coding rat SLC-1.

[SEQ ID NO : 3] shows an entire amino acid sequence of rat SLC-1.

10 [SEQ ID NO : 4] shows an entire base sequence of rat SLC-1cDNA wherein Sal I recognition sequence was added to the 5' side, and Spe I recognition sequence was added to the 3' side.

[SEQ ID NO : 5] shows riboprobe used to determine the quantity of SLC-1mRNA expressed in each clone of rat SLC-1 expression CHO cells.

15 [SEQ ID NO : 6] shows a synthetic DNA used to obtain cDNA for coding of human SLC-1.

[SEQ ID NO : 7] shows a primer used to make double-strand cDNA for coding human SLC-1.

[SEQ ID NO : 8] shows an entire base sequence of cDNA for coding human SLC-1.

20 [SEQ ID NO : 9] shows an entire amino acid sequence of human SLC-1.

[SEQ ID NO : 10] shows a synthetic DNA used for screening of cDNA for coding human SLC-1(S).

25 [SEQ ID NO : 11] shows a synthetic DNA used for screening of cDNA for coding human SLC-1(S).

[SEQ ID NO : 12] shows a synthetic DNA used for screening of cDNA for coding human SLC-1(L).

30 [SEQ ID NO : 13] shows a synthetic DNA used for screening of cDNA for coding human SLC-1(L).

[SEQ ID NO : 14] shows an entire base sequence of human SLC-1(S) cDNA wherein Sal I recognition sequence was added to the 5' side, and Spe I recognition sequence was added to the 3' side.

35 [SEQ ID NO : 15] shows an entire base sequence of human SLC-1(L) cDNA wherein Sal I recognition sequence was added

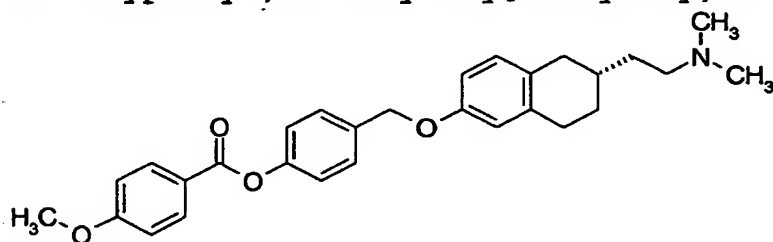
to the 5' side, and Spe I recognition sequence was added to the 3' side.

[SEQ ID NO : 16] shows riboprobe used to determine the quantity of SLC-1mRNA expressed in each clone of human
5 SLC-1(S) expression CHO cells and SLC-1(L) expression CHO cells.

Transformant *Escherichia coli* DH10B/phSLC1L8 transformed by plasmid containing DNA which codes the base
10 sequence shown by SEQ ID NO : 9, obtained in Reference Example 1 - 6, is on deposit with National Institute of Bioscience and Human-Technology (NIBH), Agency of Industrial Science and Technology, Ministry of International Trade and Industry, as deposit number FERM
15 BP-6632 from February 1, 1999; and with the Institute for Fermentation, Osaka, Japan (IFO), as deposit number IFO 16254 from January 21, 1999.

Reference Example 1

20 2-(R)-[2-(N,N-Dimethylamino)ethyl]-6-(4-[(4-methoxyphenyl)carbonyloxy]benzyloxy)tetralin



Diethyl azodicarboxylate (40% toluene solution, 0.95 g) was added dropwise to THF solution (6 ml) of 2-(R)-
25 [2-(N,N-dimethylamino)ethyl]-6-hydroxytetralin (300 mg), 4-(hydroxymethyl)phenyl 4-methoxybenzoate (530 mg), and triphenylphosphine (430 mg) under ice-cooling. After stirring for 2 hours at room temperature, the reaction mixture was concentrated. The residue was purified using
30 alumina column chromatography (development solvent; hexane ~ hexane : ethyl acetate = 10:1), and the titled compound

(320 mg) was obtained after recrystallization (ethyl acetate-hexane).

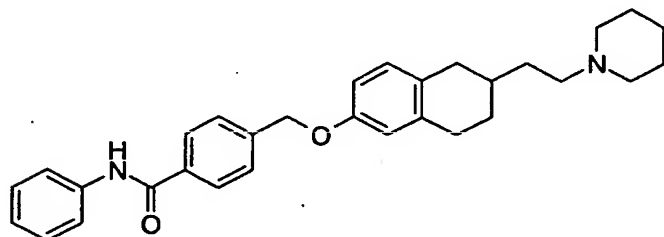
Melting point: 111 - 114°C

$[\alpha]_D^{20} = +44.4^\circ$ (c = 0.502, methanol)

5

Reference Example 2

N-Phenyl-4-[[2-(2-piperidinoethyl)-6-tetralinyl]oxymethyl]benzamide



10 Triethylamine (0.11 ml) was added to THF suspension (3 ml) of 4-[[2-(2-piperidinoethyl)-6-tetralinyl]oxymethyl]benzoate (300 mg). Further, THF solution (0.5 ml) of trimethylacetyl chloride (92 mg) was added dropwise under ice-cooling, which was stirred for 30
15 minutes. The temperature of the reaction mixture was raised to room temperature, which was stirred for 1 hour.

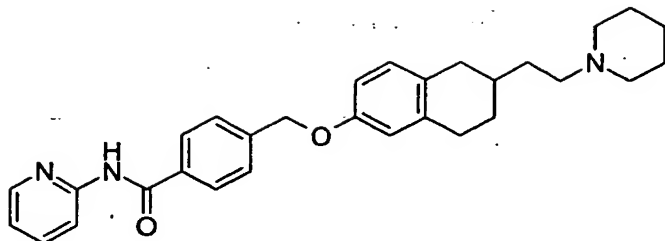
THF solution (0.5 ml) of aniline (85 mg) was added dropwise to the reaction mixture under ice-cooling, which was stirred for 1 hour. After the reaction mixture was stirred
20 for 24 hours at room temperature, saturated sodium bicarbonate solution was added, and extraction was conducted using a mixed solution of ethyl acetate and THF.

The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then
25 concentrated. The residue was recrystallized from THF-methanol-IPE to give the titled compound (150 mg).

Melting point: 183 - 185°C

Reference Example 3

30 4-[[2-(2-Piperidinoethyl)-6-tetralinyl]oxymethyl]-N-(2-pyridinyl)benzamide



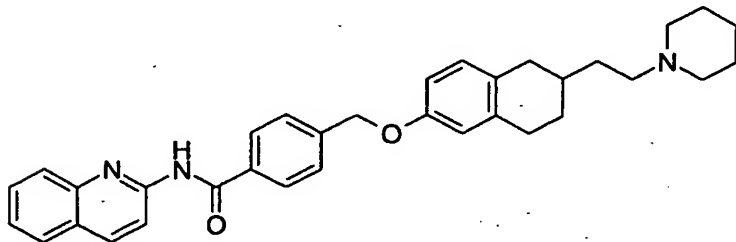
Triethylamine (0.11 ml) was added to THF suspension (6 ml) of 4-[[2-(2-piperidinoethyl)-6-tetralinyl]oxymethyl]benzoate (300 mg). Trimethylacetyl chloride (0.095 ml) was added dropwise to the obtained suspension under ice-cooling, which was stirred for 30 minutes. The temperature of the reaction mixture was raised to room temperature, which was stirred for 1 hour.

THF solution (1.0 ml) of 2-aminopyridine (110 mg) was added dropwise to the reaction mixture under ice-cooling, which was stirred for 1 hour. Then the reaction mixture was stirred at room temperature for 6 hours, and at 60°C for 12 hours, which was refluxed with heating for 6 hours.

Saturated sodium bicarbonate solution was added to the reaction mixture, and extraction was conducted using ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was purified using alumina column chromatography (development solvent: THF), and recrystallized (ethyl acetate-IPE) to give the titled compound (30 mg).

Reference Example 4

4-[[2-(2-Piperidinoethyl)-6-tetralinyl]oxymethyl]-N-(2-quinolinyloxy)benzamide

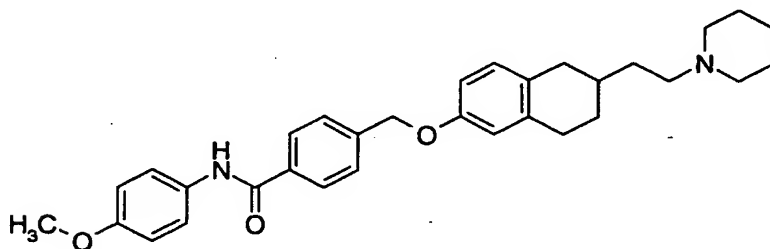


Triethylamine (0.22 ml) was added to THF suspension (6 ml) of 4-[[2-(2-piperidinoethyl)-6-tetralinyl]oxymethyl]benzoate (300 mg). Further, trimethylacetyl chloride (0.095 ml) was added dropwise to under ice-cooling, which was stirred for 30 minutes. The temperature of the reaction mixture was raised to room temperature, which was stirred for 1 hour. THF solution (1.0 ml) of 2-aminoquinoline (170 mg) was added dropwise to the reaction mixture under ice-cooling, which was stirred at room temperature for 12 hours. Saturated sodium bicarbonate solution was added to the reaction mixture, and extraction was conducted using ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was purified using alumina column chromatography (development solvent: THF), and recrystallized (ethyl acetate-diisopropyl ether) to give the titled compound (45 mg).

Melting point: 135 - 138°C

Reference Example 5

N-(4-Methoxyphenyl)-4-[[2-(2-piperidinoethyl)-6-tetralinyl]oxymethyl]benzamide



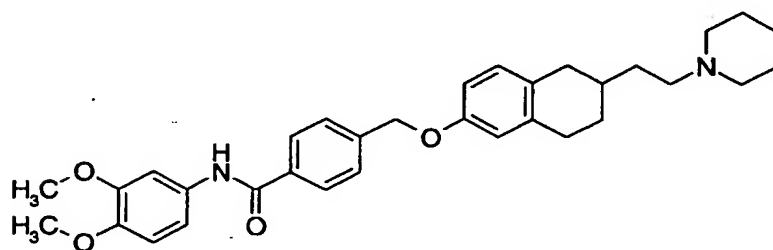
WSCD (0.11 ml) was added to DMF solution (2 ml) of 4-[[2-(2-piperidinoethyl)-6-tetralinyl]oxymethyl]benzoate (170 mg), 4-methoxyaniline (53 mg), HOBt (70 mg) and DMAP (60 mg) at room temperature, which was stirred for 12 hours. 10% aqueous potassium carbonate solution and water was added to the reaction mixture, and extraction was conducted using a mixed

solution of THF and ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was purified using alumina column chromatography (development solvent: THF), and recrystallized (THF-IPE) to give the

5 titled compound (140 mg).
Melting point: 193 - 196°C

Reference Example 6

10 N-(3,4-Dimethoxyphenyl)-4-[[2-(2-piperidinoethyl)-6-tetralinyl]oxymethyl]benzamide

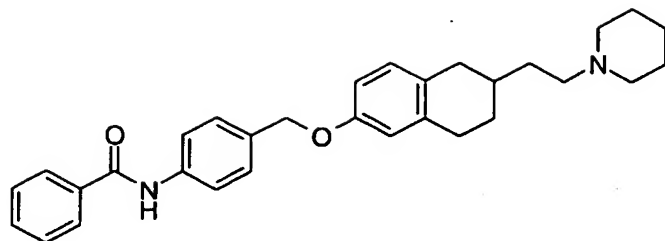


WSCD (free form, 0.2 ml) was added to DMF solution (3 ml) of 4-[[2-(2-piperidinoethyl)-6-tetralinyl]oxymethyl]benzoate (300 mg), 3,4-dimethoxyaniline (120 mg), HOBt (120 mg) and DMAP (100 mg) at room temperature, which was stirred for 12 hours. 10% aqueous potassium carbonate solution was added to the reaction mixture, and the resulting crystals were collected by filtration. The crystals were washed with water, then dried. The crystals were purified using alumina column chromatography (development solvent; THF), and recrystallized (THF-IPE) to give the titled compound (330 mg).

25 Melting point: 178 - 180°C

Reference Example 7

6-[4-(Benzoylamino)benzyloxy]-2-(2-piperidinoethyl)tetralin



Sodium hydride (60% oily, 85 mg) was added to DMF solution of 6-hydroxy-2-(2-piperidinoethyl)tetralin (500 mg) at room temperature, which was stirred for 1 hour.

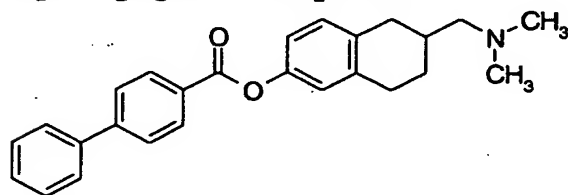
5 N-[4-(bromomethyl)phenyl]benzamide (670 mg) was added to the reaction mixture at room temperature, which was stirred for 1 hour. Water was added to the reaction mixture, and extraction was conducted using ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was purified using alumina column chromatography (development solvent : THF), and recrystallized (ethyl acetate) to give the titled compound (200 mg).

Melting point: 176 - 179° C

15

Reference Example 8

2-[(N,N-Dimethylamino)methyl]-6-tetralinyl 4-biphenylcarboxylate



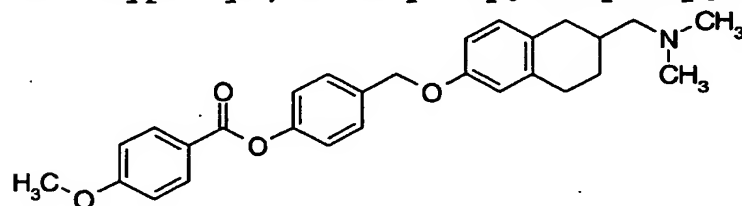
20 4-Biphenylylcarboxylic acid (580 mg) and WSC (560 mg) were added to pyridine solution (6 ml) of 2-[(N,N-dimethylamino)methyl]-6-hydroxytetralin (300 mg), which was stirred at room temperature for 36 hours. Saturated sodium bicarbonate solution and water were added to the
25 reaction mixture, and extraction was conducted using ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then

concentrated. The residue was purified using alumina column chromatography (development solvent; hexane - hexane:ethyl acetate = 10:1), and recrystallized (hexane) to give the titled compound (300 mg).

5 Melting point: 85 - 86°C

Reference Example 9

2-[(N,N-Dimethylamino)methyl]-6-[4-[(4-methoxyphenyl)carbonyloxy]benzyloxy]tetralin



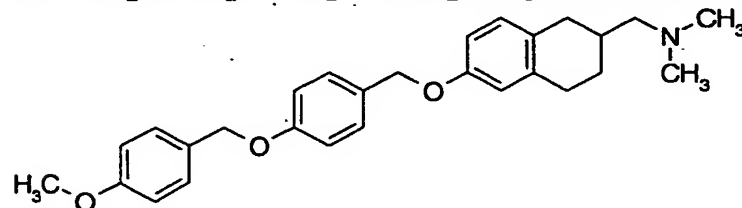
10

Diethyl azodicarboxylate (40% toluene solution, 950 mg) was added dropwise to THF solution (3 ml) of 2-[(N,N-dimethylamino)methyl]-6-hydroxytetralin (150 mg), 4-(hydroxymethyl)phenyl 4-methoxybenzoate (570 mg) and triphenylphosphine (574 mg) at room temperature, which was stirred for 3 hours. The reaction mixture was concentrated, and the residue was purified using alumina column chromatography (development solvent; hexane - hexane:ethyl acetate = 6:1), and recrystallized (ethyl acetate-hexane) to give the titled compound (175 mg).
 15
 20 Melting point: 119 - 121°C

Reference Example 10

2-[(N,N-Dimethylamino)methyl]-6-[4-[(4-methoxybenzyl)oxy]benzyloxy]tetralin

25

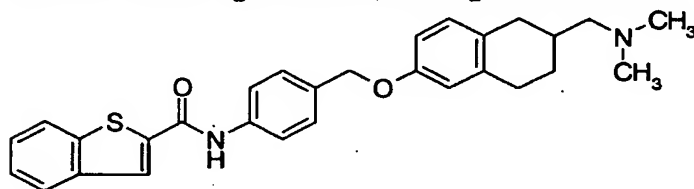


Diethyl azodicarboxylate (40% toluene solution, 1.91 g) was added dropwise to THF solution (6 ml) of 2-

[(N,N-dimethylamino)methyl]-6-hydroxytetralin (300 mg),
4-[(4-methoxybenzyl)oxy]benzylalcohol (1.07 g) and
triphenylphosphine (1.15g) at room temperature, which was
stirred for 12 hours. The reaction mixture was
concentrated, and the residue was purified using alumina
column chromatography (development solvent; hexane -
hexane:ethyl acetate = 10:1), and recrystallized (ethyl
acetate-hexane) to give the titled compound (260 mg).
Melting point: 106 - 111°C

Reference Example 11

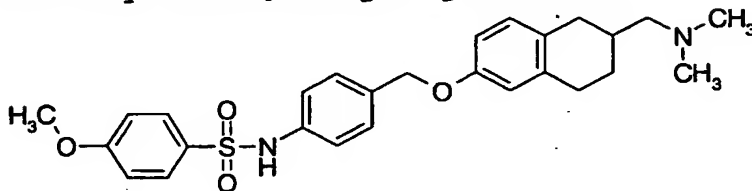
6-[4-[(1-Benzothiophen-2-yl)carbonylamino]benzyloxy]-2-
[(N,N-dimethylamino)methyl]tetralin



One drop of DMF was added to THF solution (4 ml) of
1-benzothiophene-2-carboxylic acid (230 mg), and oxalyl
chloride (0.23 ml) was further added under ice-cooling,
which was stirred for 30 minutes at room temperature. The
reaction mixture was concentrated, which was dissolved in
THF (1 ml). The obtained solution was added dropwise to
pyridine solution (6 ml) of 6-(4-aminobenzyloxy)-2-
[(N,N-dimethylamino)methyl]tetralin (300 mg), which was
stirred for 15 minutes. After stirring at room temperature
for another 15 minutes, 10% aqueous potassium carbonate
solution was added to the reaction mixture, and extraction
was conducted using ethyl acetate. The organic layer was
washed with water and saturated aqueous sodium chloride
solution, dried, and then concentrated. The residue was
purified using alumina column chromatography (development
solvent; ethyl acetate), and recrystallized (THF-IPE) to
give the titled compound (250 mg).
Melting point: 165 - 169°C

Reference Example 12

2-[(N,N-Dimethylamino)methyl]-6-[4-[(4-methoxyphenyl)sulfonylamino]benzyloxy]tetralin



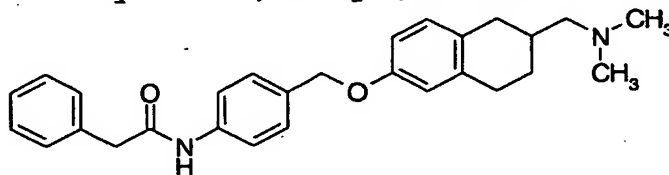
5

THF solution (1 ml) of 4-methoxybenzenesulfonyl chloride (270 mg) was added dropwise to pyridine solution (6 ml) of 6-[(4-aminobenzyl)oxy]-2-[(N,N-dimethylamino)methyl]tetralin (300 mg) under ice-cooling, which was stirred for 15 minutes. After stirring at room temperature for further 15 minutes, 10% aqueous potassium carbonate solution was added to the reaction mixture, and extraction was conducted using ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was purified using alumina column chromatography (development solvent: ethyl acetate), and recrystallized (ethyl acetate-IPE) to give the titled compound (260 mg). Melting point: 137 - 140°C

20

Reference Example 13

6-[4-(Benzylcarbonylamino)benzyloxy]-2-[(N,N-dimethylamino)methyl]tetralin



25

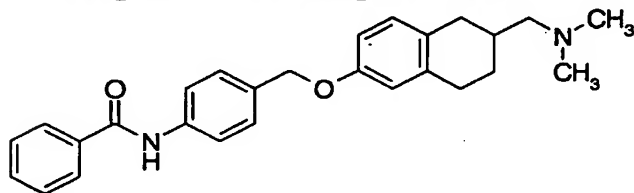
THF solution (1 ml) of phenylacetyl chloride (200 mg) was added dropwise to pyridine solution (6 ml) of 6-[(4-aminobenzyl)oxy]-2-[(N,N-dimethylamino)methyl]tetralin (300 mg) under ice-cooling, which was stirred for 15 minutes. After stirring at room temperature for further 15 minutes, saturated sodium

30

bicarbonate solution was added to the reaction mixture, and extraction was conducted using ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was purified using alumina column chromatography (development solvent; hexane ~ hexane:ethyl acetate = 2:1), and recrystallized to give the titled compound (175 mg). Melting point: 130 - 135°C

10 Reference Example 14

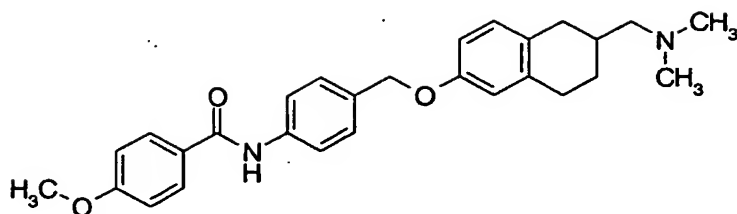
6-[4-(Benzoylamino)benzyloxy]-2-[(N,N-dimethylamino)methyl] tetralin



Benzoyl chloride (0.14 ml) was added dropwise to pyridine solution (6 ml) of 6-[(4-aminobenzyl)oxy]-2-[(N,N-dimethylamino)methyl]tetralin (300 mg) under ice-cooling, which was stirred at room temperature for 30 minutes. 10% aqueous potassium carbonate solution was added to the reaction mixture, and extraction was conducted using ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was purified using alumina column chromatography (development solvent; ethyl acetate), and recrystallized (THF-IPE) to give the titled compound (240 mg). Melting point: 128 - 133°C

Reference Example 15

2-[(N,N-Dimethylamino)methyl]-6-[4-[(4-methoxybenzoyl)amino]benzyloxy]tetralin

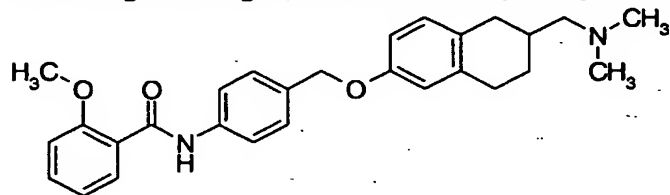


p-Anisoyl chloride (0.20 ml) was added dropwise to pyridine solution (6 ml) of 6-[(4-aminobenzyl)oxy]-2-[(N,N-dimethylamino)methyl]tetralin (300 mg) under ice-cooling, which was stirred at room temperature for 30 minutes. 10% aqueous potassium carbonate solution was added to the reaction mixture, and extraction was conducted using ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was purified using alumina column chromatography (development solvent: ethyl acetate), and recrystallized (THF-IPE) to give the titled compound (300 mg).

Melting point: 155 - 159°C

Reference Example 16

2-[(N,N-Dimethylamino)methyl]-6-[4-[(2-methoxybenzoyl)amino]benzyloxy]tetralin



o-Anisoyl chloride (0.15 ml) was added dropwise to pyridine solution (4 ml) of 6-[(4-aminobenzyl)oxy]-2-[(N,N-dimethylamino)methyl]tetralin (200 mg) under ice-cooling, which was stirred at room temperature for 30 minutes. 10% aqueous potassium carbonate solution was added to the reaction mixture, and extraction was conducted using ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was purified

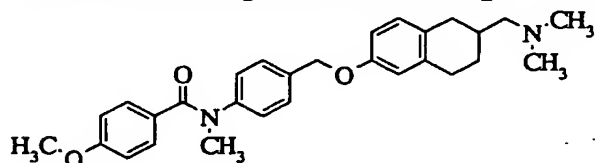
using alumina column chromatography (development solvent; THF), and recrystallized (ethyl acetate-hexane) to give the titled compound (200 mg).

Melting point: 106 - 108° C

5

Reference Example 17

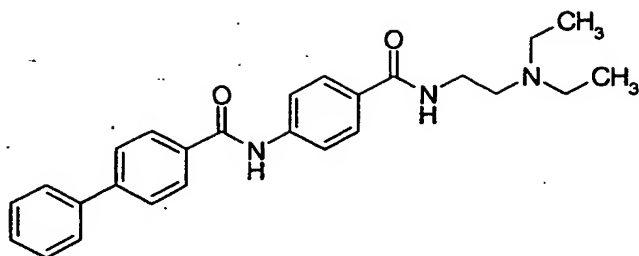
6-[4-[N-(4-Methoxybenzoyl)-N-methylamino]benzyloxy]-2-
[(N,N-dimethylamino)methyl]tetralin



Diethyl azodicarboxylate (40% toluene solution, 960 mg) was added dropwise to THF solution (3 ml) of 2-[(N,N-dimethylamino)methyl]-6-hydroxytetralin (150 mg), N-[4-(hydroxymethylphenyl)-4-methoxy-N-methylbenzamide (600 mg) and triphenylphosphine (570 mg) at room temperature, which was stirred for 12 hours. After the reaction mixture was concentrated, the residue was purified using silica gel column chromatography (development solvent; hexane - ethyl acetate - ethyl acetate:methanol = 1:2), and then purified using alumina column chromatography (development solvent; hexane - hexane:ethyl acetate = 2:1) to give the titled compound (185 mg). ¹H-NMR (CDCl₃) δ: 1.20-1.50(1H, m), 1.80-2.46(5H, m), 2.25(6H, s), 2.68-2.86(3H, m), 3.47(3H, s), 3.74(3H, s), 4.95(2H, s), 6.52-6.76(4H, m), 6.84-7.14(3H, m), 7.22-7.38(4H, m).

Reference Example 18

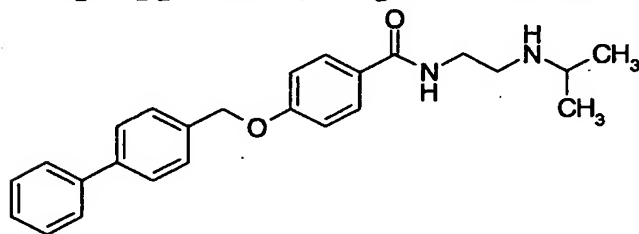
N-[4-[[[2-(Diethylamino)ethyl]amino]carbonyl]phenyl] 4-biphenylylcarboxamide



Oxalyl chloride (0.46 ml) and DMF (1 drop) were added to THF solution (15 ml) of 4-biphenylcarboxylic acid (0.879g) under ice-cooling. The reaction mixture was stirred at room temperature for 30 minutes, and concentrated. The residue was dissolved in THF (10 ml), which was added dropwise to THF (20 ml) suspension of procaineamide hydrochloride (1.078 g) and triethylamine (1.4 ml) at 0°C. After stirring at 0°C for 30 minutes, 10% aqueous potassium carbonate solution was added to the reaction mixture, and extraction was conducted using ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was recrystallized using methanol to give the titled compound (1.147 g). Melting point: 237 - 240°C (decomposition)

Reference Example 19

4-(4-Biphenylmethoxy)-N-[2-(isopropylamino)ethyl]benzamide



WSC (0.708 g), HOBt (0.521 g), N-isopropyl ethylenediamine (0.353 g) and triethylamine (1 ml) were added to a mixed solution of 4-(4-biphenylmethoxy) benzoate (1.007 g) in THF (30 ml) and acetonitrile (30 ml). After stirring at room temperature for 18 hours, water was added to the reaction mixture, and extraction was conducted

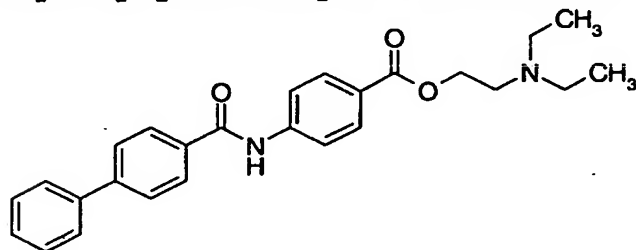
using ethyl acetate. The organic layer was washed with 10% aqueous potassium carbonate solution and saturated aqueous sodium chloride solution, dried, and then concentrated.

The residue was recrystallized using ethanol to give the
5 titled compound (0.806 g).

Melting point: 150 - 154°C

Reference Example 20

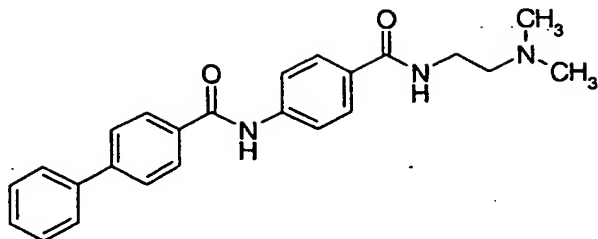
2-(N,N-Diethylamino)ethyl 4-(4-
10 biphenylcarbonylamino)benzoate



Oxalyl chloride (0.39 ml) and DMF (1 drop) were added to THF solution (15 ml) of 4-biphenylcarboxylic acid (1.091 g) under ice-cooling, which was stirred at room
15 temperature for 30 minutes, and concentrated. The residue was dissolved in THF (10 ml), which was added dropwise to THF suspension (30 ml) of procaine hydrochloride (1.091 g) and triethylamine (0.67 ml) at 0°C. After stirring at 0°C for 30 minutes, 10% aqueous potassium carbonate was added
20 to the reaction mixture, and extraction was conducted using ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was recrystallized using ethyl acetate/hexane to give the titled compound (0.728 g).
25 Melting point: 146 - 149°C

Reference Example 21

N-[4-[[[2-(Dimethylamino)ethyl]amino]carbonyl]phenyl]
4-biphenylcarboxamide



WSC (0.248 g), HOBt (0.156 g), N,N-dimethyl ethylenediamine (0.097 g) and triethylamine (0.21 ml) were added to a mixed solution of 4-(4-

5 biphenylcarbamoylamino)benzoate (0.323 g) in THF (15 ml) and acetonitrile (15 ml). After stirring at room temperature for 18 hours, water was added to the reaction mixture, and extraction was conducted using ethyl acetate.

The organic layer was washed with 10% aqueous potassium carbonate and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was recrystallized using methanol/diethyl ether to give the titled compound (0.100 g).

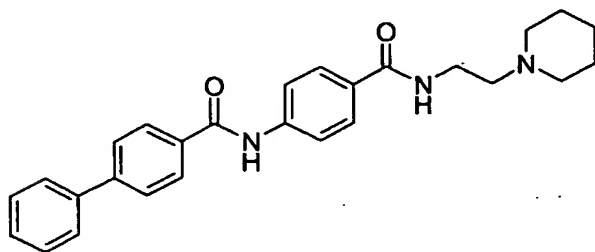
Melting point: 261 - 264°C (decomposition)

15

The compounds described in the following Reference Examples 22 to 25 were produced in the same manner as in Reference Example 21.

20 Reference Example 22

N-[4-[[2-(Piperidinoethyl)amino]carbonyl]phenyl] 4-biphenylcarboxamide

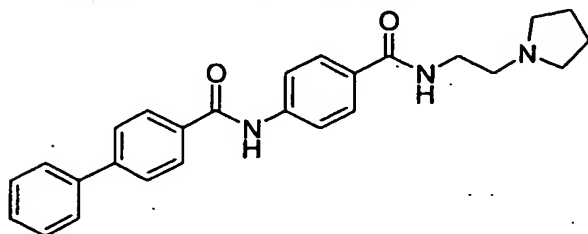


Melting point: 247 - 252°C (decomposition)

25

Reference Example 23

N-[4-[[2-(1-Pyrrolidinyl)ethyl]amino]carbonyl]phenyl]
4-biphenylylcarboxamide

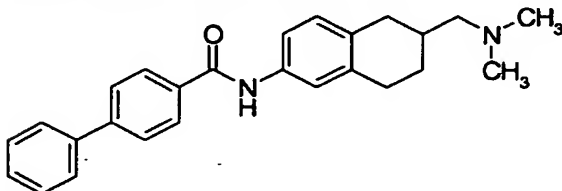


Melting point: 241 - 245°C (decomposition)

5

Reference Example 24

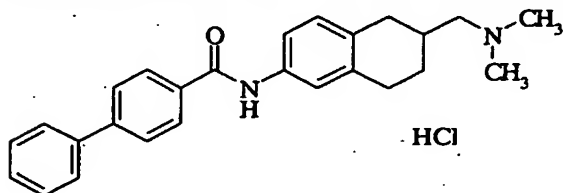
N-[2-(N,N-Dimethylamino)methyl-6-tetralinyl]-4-
biphenylylcarboxamide



10 Melting point: 164 - 166°C

Reference Example 25

N-[2-(N,N-Dimethylamino)methyl-6-tetralinyl]-4-
biphenylylcarboxamide hydrochloride



15

Melting point: >250°C

¹H-NMR δ : 1.24-1.54 (1H, m), 1.84-2.10 (2H, m), 2.20-2.50 (3H, m), 2.26 (6H, s), 2.79-3.01 (3H, m), 7.10 (1H, d, J=8Hz), 7.28-7.54 (5H, m), 7.60-7.82 (5H, m), 7.94 (2H, d, J=8Hz).

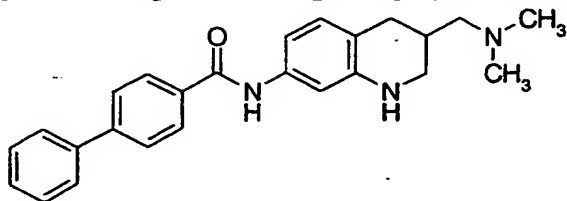
20

IR(KBr) 3028, 2910, 2640, 1658, 1538, 1417, 746, 701 cm⁻¹

Reference Example 26

N-[3-[(N,N-Dimethylamino)methyl]-1,2,3,4-tetrahydro-7-

quinolinyll]-4-biphenylylcarboxamide

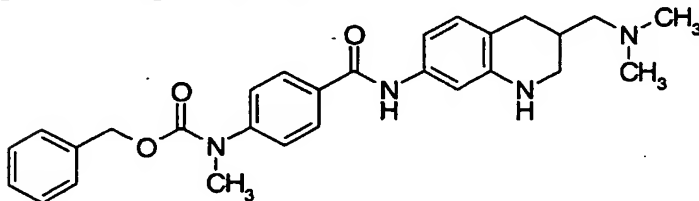


One drop of DMF was added to THF solution of 4-biphenylylcarboxylic acid (145 mg), and oxalyl chloride (0.1 ml) was added dropwise to the solution under ice-cooling, which was stirred at room temperature for 30 minutes. After the reaction mixture was concentrated, the residue was dissolved in THF (1 ml), which was added dropwise to pyridine solution (1.5 ml) of 7-amino-3-[(N,N-dimethylamino)methyl]-1,2,3,4-tetrahydroquinoline (150 mg) under ice-cooling, and the reaction mixture was stirred for 30 minutes. After the temperature of the reaction mixture was raised to room temperature, 10% aqueous potassium carbonate was added to the reaction mixture, and extraction was conducted using a mixed solution of THF and ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was recrystallized using THF-IPE to give the titled compound (180 mg).

Melting point: 206 - 211°C

Reference Example 27

4-[N-[(Benzyloxy)carbonyl]-N-methylamino]-N-[3-[(N,N-dimethylamino)methyl]-1,2,3,4-tetrahydro-7-quinolinyll]benzamide



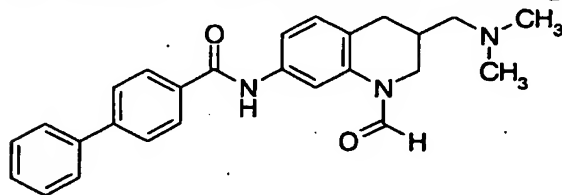
One drop of DMF was added dropwise to THF solution (2

ml) of 4-[N-[(benzyloxy)carbonyl]-N-methylamino]benzoic acid (210 mg), and then oxalyl chloride (0.1 ml) was added dropwise under ice-cooling, which was stirred at room temperature for 30 minutes. After the reaction mixture was concentrated, the residue was dissolved in THF (1 ml), which was added dropwise to pyridine solution (1.5 ml) of 7-amino-3-[(N,N-dimethylamino)methyl]-1,2,3,4-tetrahydroquinoline (150 mg) under ice-cooling. The reaction mixture was then stirred for 30 minutes. After the temperature of the reaction mixture was raised to room temperature, 10% aqueous potassium carbonate solution was added, and extraction was conducted using a mixed solution of THF and ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was recrystallized using THF-IPE to give the titled compound (220 mg).

Melting point: 167 - 172°C

Reference Example 28

N-[3-[(N,N-Dimethylamino)methyl]-1-formyl-1,2,3,4-tetrahydro-7-quinolinyl]-4-biphenylcarboxamide



Anhydrous acetic acid (0.1 ml) was added to formic acid (1 ml), which was stirred at 55°C for 2 hours. N-[3-[(N,N-dimethylamino)methyl]-1,2,3,4-tetrahydro-7-quinolinyl]-4-biphenylcarboxamide (80 mg) was added to the reaction mixture under ice-cooling, which was stirred at room temperature for 72 hours. 10% aqueous potassium carbonate solution was added to the reaction mixture to make the mixture alkaline, and extraction was conducted using ethyl acetate. The organic layer was washed with water and

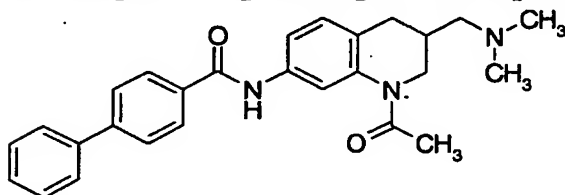
saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was recrystallized using THF-IPE to give the titled compound (80 mg).

Melting point: 134 - 138°C

5

Reference Example 29

N-[1-Acetyl-3-[(N,N-dimethylamino)methyl]-1,2,3,4-tetrahydro-7-quinolyl]-4-biphenylcarboxamide



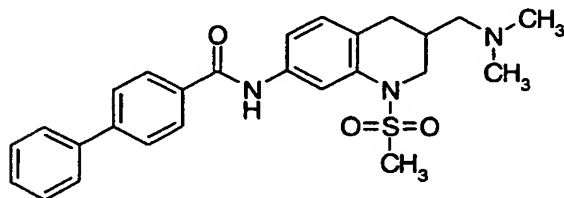
10 Acetyl chloride (0.02 ml) was added to pyridine solution (1 ml) of N-[3-[(N,N-dimethylamino)methyl]-1,2,3,4-tetrahydro-7-quinolyl]-4-biphenylcarboxamide (80 mg) under ice-cooling, which was stirred for 15 minutes, and then stirred at room temperature for 15 minutes. 10% aqueous potassium carbonate solution was added to the reaction mixture, and extraction was conducted using ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was recrystallized using THF-IPE to give the titled compound (64 mg).

15

Melting point: 167 - 173°C

Reference Example 30

25 N-[3-[(N,N-Dimethylamino)methyl]-1-methylsulfonyl-1,2,3,4-tetrahydro-7-quinolyl]-4-biphenylcarboxamide



Methanesulfonyl chloride (0.02 ml) was added to

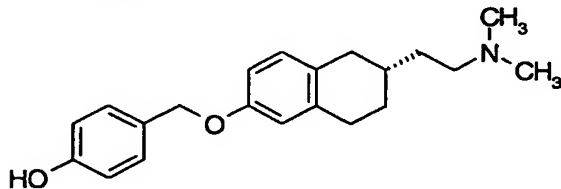
pyridine solution (1 ml) of N-[3-[(N,N-dimethylamino)methyl]-1,2,3,4-tetrahydro-7-quinoliny]-4-biphenylcarboxamide (80 mg) under ice-cooling, which was stirred at room temperature for 1 hour. Further,
5 methanesulfonyl chloride (0.02 ml) was added to the reaction mixture under ice-cooling, which was stirred at room temperature for 12 hours. 10% aqueous potassium carbonate solution was added to the reaction mixture, and extraction was conducted using ethyl acetate. The organic
10 layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was recrystallized using THF-IPE to give the titled compound (64 mg).

Melting point: 184 - 188°C

15

Reference Example 31

2-(R)-[2-(N,N-Dimethylamino)ethyl]-6-(4-hydroxyphenyl) methoxytetralin



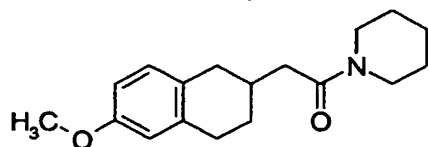
20 THF solution (2 ml) of 2-(R)-[2-(N,N-dimethylamino)ethyl]-6-[4-(4-methoxyphenylcarbonyloxy)phenylmethoxy]tetralin (330 mg) was added dropwise to THF suspension (4 ml) of lithium aluminum hydride (60 mg) under ice-cooling. 1N aqueous sodium hydroxide solution was
25 added the reaction mixture to make the mixture basic, and the precipitate was removed by celite filtration. After the filtrate was concentrated, the residue was purified using silica gel chromatography (development solvent; ethyl acetate - methanol), and recrystallized (ethyl
30 acetate-hexane) to give the titled compound (70 mg).

Melting point: 132 - 135°C

$[\alpha]_D^{20} = +56.9^\circ$ (c = 0.505, methanol)

Reference Example 32

2-(6-Methoxy-2-tetralinyl)-1-piperidino-1-ethanone

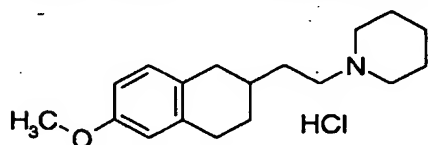


5 2-(6-Methoxy-2-tetralinyl)acetic acid (8.8 g) was dissolved in a mixed solution of THF (150 ml) and acetonitrile (50 ml), then piperidine (5.2 g), WSC (12 g), HOBT (6.0 g) and triethylamine (17 ml) were added to the solution, which was stirred at room temperature for 12
10 hours. Water was added to the reaction mixture, and extraction was conducted using ethyl acetate. The organic layer was washed with 1N hydrochloric acid, water, saturated sodium bicarbonate solution, water, and saturated aqueous sodium chloride solution, dried, and then
15 concentrated. The residue was purified using silica gel chromatography (development solvent; ethyl acetate) to give the titled compound (10.3 g). Recrystallization from hexane gave crystals of the following melting points. Melting point: 59 - 61°C

20

Reference Example 33

6-Methoxy-2-(2-piperidinoethyl)tetralin hydrochloride



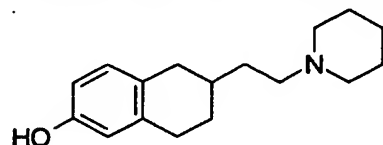
THF solution (50 ml) of 2-(6-methoxy-2-
25 tetralinyl)-1-piperidino-1-ethanone (9.80 g) was added dropwise to THF suspension (100 ml) of lithium aluminum hydride (1.94 g) under ice-cooling. The temperature of the reaction mixture was raised to 60°C over 30 minutes, which was stirred for 30 minutes. After the reaction mixture was
30 cooled to room temperature, 1N aqueous sodium hydroxide solution was added to make the reaction mixture basic, and

the precipitate was removed by celite filtration. The filtrate was concentrated and the residue was made into a hydrochloride, which was then recrystallized from ethanol-IPE to give the titled compound (9.80 g).

5 Melting point: 189 - 191°C

Reference Example 34

6-Hydroxy-2-(2-piperidinoethyl)tetralin



10 6-Methoxy-2-(2-piperidinoethyl)tetralin

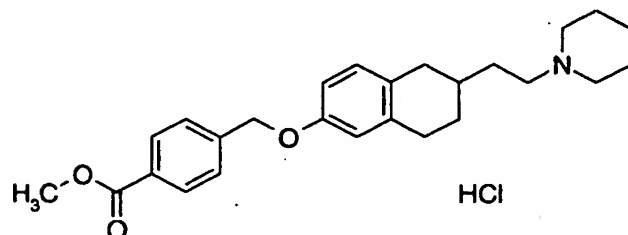
hydrochloride (9.3 g) was added to 48% hydrobromic acid (50 ml), which was refluxed with heating for 4 hours. After the reaction mixture was concentrated under reduced pressure, saturated sodium bicarbonate solution was added to the residue to make the water layer alkaline, and the water layer was extracted using a mixed solution of THF and ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The resulting crystal was washed with IPE to give the titled compound (5.8 g).

20 Melting point: 154 - 157°C

Reference Example 35

Methyl 4-[[2-(2-piperidinoethyl)-6-

25 tetralinyl]oxymethyl]benzoate hydrochloride



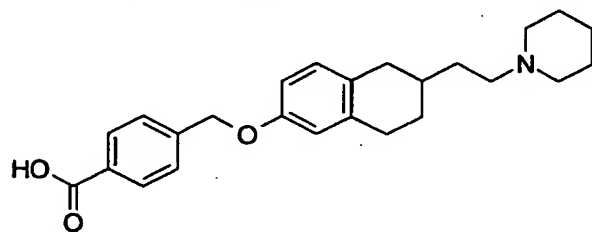
Diethyl azodicarboxylate (40% toluene solution, 5.10 g) was added dropwise to THF solution (15 ml) of 6-hydroxy-2-(2-piperidinoethyl)tetralin (1.50 g), methyl

4-(hydroxymethyl)benzoate (1.44 g), and triphenylphosphine (2.60 g) at room temperature, which was stirred for 12 hours, and then concentrated. The residue was purified using aluminum column chromatography (development solvent; hexane ~ hexane:ethyl acetate = 15:1), which was made into a hydrochloride. The hydrochloride was recrystallized (methanol-IPE) to give the titled compound (1.36 g).

Melting point: 190 - 193°C.

Reference Example 36

4-[[2-(2-Piperidinoethyl)-6-tetralinyl]oxymethyl]benzoic acid

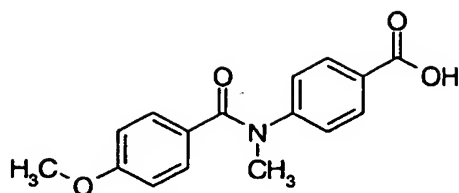


3N Aqueous sodium hydroxide solution (1.8 ml) was added to methanol solution (20 ml) of methyl 4-[[2-(2-piperidinoethyl)-6-tetralinyl]oxymethyl]benzoate hydrochloride (1.06 g), which was refluxed with heating for 6 hours. After the reaction mixture was concentrated, water was added to the reaction mixture. Further, 1N hydrochloric acid was added to make the pH of the mixture about 7. The resulting crystals were filtered to give the titled compound (0.93 g). Recrystallization from ethanol gave crystals of the following melting points.

Melting point: 105 - 108°C

Reference Example 37

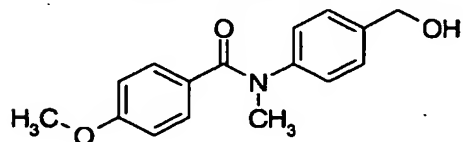
4-[N-(4-Methoxybenzoyl)-N-methylamino]benzoic acid



Aqueous solution (50 ml) of sodium carbonate (23 g) was added to THF solution (50 ml) of 4-(methylamino)benzoic acid (5.0 g), and p-anisoyl chloride (5.6 g) was added dropwise to the solution under ice-cooling, which was stirred for 15 minutes, and then stirred at room temperature for 30 minutes. Concentrated hydrochloric acid was added to the reaction mixture under ice-cooling to make the water layer acidic, and extraction was conducted using ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was purified using silica gel column chromatography (development solvent; hexane - hexane:ethyl acetate = 1:2), and recrystallized (ethyl acetate-hexane) to give the titled compound (4.8 g). Melting point: 157 - 160°C.

Reference Example 38

N-[4-(Hydroxymethyl)phenyl]-4-methoxy-N-methylbenzamide



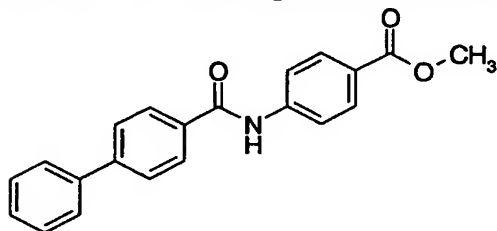
THF solution (1M, 16 ml) of borane was added dropwise to THF solution (10 ml) of 4-[N-(4-methoxybenzoyl)-N-methylamino]benzoic acid (1.14 g) under ice-cooling, which was stirred for 15 minutes, and then stirred at room temperature for 1 hour. After water was added to the reaction mixture, 1N hydrochloric acid was further added, and extraction was conducted using ethyl acetate. The organic layer was washed with water and saturated sodium bicarbonate, and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was

purified using silica gel chromatography (development solvent; hexane ~ hexane:ethyl acetate = 1:2), and recrystallized (ethyl acetate-hexane) to give the titled compound (770 mg).

5 Melting point: 85 - 90° C.

Reference Example 39

Methyl 4-(4-biphenylcarbonylamino)benzoate

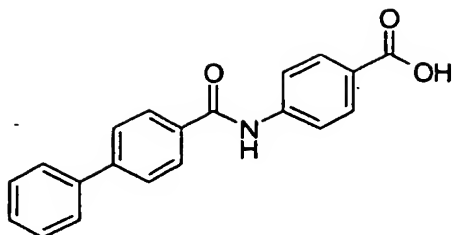


10 Oxalyl chloride (1.2 ml) and DMF (0.04 ml) were added to THF solution (30 ml) of 4-biphenylcarboxylic acid (2.184g) under ice-cooling. The reaction mixture was stirred at room temperature for 30 minutes, which was concentrated. The residue was dissolved in THF (15 ml),
15 which was added dropwise to THF solution (30 ml) of methyl 4-aminobenzoate (1.512 g) and triethylamine (2.1 ml) at 0° C. After the reaction mixture was stirred at 0° C for 30 minutes, 10% citric acid solution was added to the reaction mixture, and extraction was conducted using ethyl acetate.
20 The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The resulting crude crystal was washed with diethyl ether to give the titled compound (2.179 g).
Melting point: 247 - 251° C.

25

Reference Example 40

4-(4-Biphenylcarbonylamino)benzoic acid

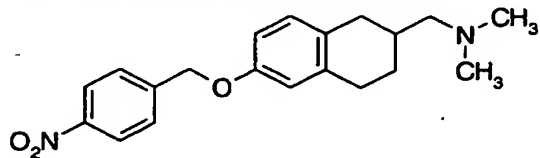


1N Aqueous sodium hydroxide solution (8 ml) was added to a mixed solution of methyl 4-(4-biphenyl)carbamoylbenzoate (1.998 g) in THF (60 ml) and methanol (20 ml), which was stirred at room temperature for 18 hours. 1N Hydrochloric acid (10 ml) was added to the reaction mixture, and extraction was conducted using ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The resulting crude crystals were washed with diethyl ether to give the titled compound (1.760 g). Melting point: >320°C.

¹H NMR (DMSO-d₆) δ: 7.37-7.57 (3H,m), 7.77 (2H,d), 7.85 (2H,d), 7.95 (4H,s), 8.08 (2H,d), 10.56 (1H,s)

Reference Example 41

2-[(N,N-Dimethylamino)methyl]-6-(4-nitrobenzyloxy)tetralin

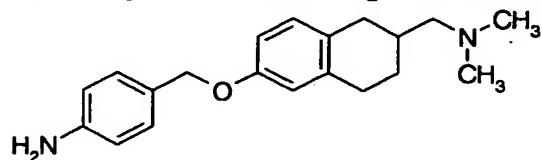


Diethyl azodicarboxylate (40% toluene solution, 9.53 g) was added dropwise to THF solution (15 ml) of 2-[(N,N-dimethylamino)methyl]-6-hydroxytetralin (1.5 g), 4-nitrobenzylalcohol (3.35 g), and triphenylphosphine (5.74 g) at room temperature, which was stirred for 24 hours. The reaction mixture was concentrated, and the residue was purified using alumina column chromatography (development solvent; hexane ~ hexane:ethyl acetate = 8:1), and recrystallized (ethyl acetate-hexane) to give the titled compound (1.29 g).

Melting point: 83 - 89° C

Reference Example 42

6-(4-Aminobenzyloxy)-2-[(N,N-
5 dimethylamino)methyl]tetralin



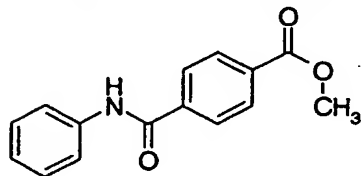
After acetic acid (6 ml) was added to THF solution (12 ml) of 2-[(N,N-dimethylamino)methyl]-6-(4-nitrobenzyloxy)tetralin (1.91 g) under ice-cooling, zinc powder (3.67 g) was further added, which was stirred for 6 hours. The reaction mixture was filtered, and the filtrate was concentrated. 10% aqueous potassium carbonate solution and ethyl acetate were added to the residue, the precipitate was removed by celite filtration, and the filtrate was extracted using ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was purified using aluminum column chromatography (development solvent; hexane - hexane:ethyl acetate = 4:1) to give the titled compound (1.05 g).

Amorphous powder:

¹H-NMR (CDCl₃) δ: 1.18-1.50(1H, m), 1.70-2.50(5H, m), 2.24(6H, s), 2.72-2.86(3H, m), 3.68(2H, brs), 4.88(2H, s), 6.58-6.82(4H, m), 6.99(1H, s), 7.14-7.30(2H, m).

Reference Example 43

Methyl 4-anilinocarbonylbenzoate

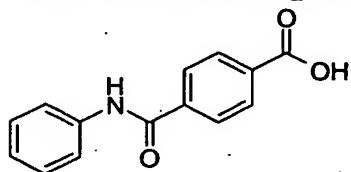


4-Methoxycarbonyl benzoic acid (540 mg), aniline (0.27 ml), WSC (863 mg) and triethylamine (0.84 ml) were

- added to THF (20 ml). After the reaction mixture was stirred at room temperature for 20 hours, the reaction mixture was placed in water, and extraction was conducted using ethyl acetate-THF (1:1). The organic layer was washed with water, saturated sodium bicarbonate solution, and saturated aqueous sodium chloride solution, dried, and then concentrated. The resulting crude crystals were recrystallized from ethyl acetate-hexane to give the titled compound (659 mg).
- 10 Melting point: 189 - 190°C

Reference Example 44

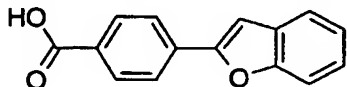
4-Anilinocarbonylbenzoic acid



- 15 8 mol of aqueous sodium hydroxide solution (8 ml) was added to methanol (16 ml) - THF (6 ml) solution of 4-methyl anilinocarbonylbenzoate (511 mg), which was stirred at room temperature for 1 hour. 1 mol of hydrochloric acid was added to the reaction mixture to make the pH of the mixture to 5; extraction was conducted using ethyl acetate-THF (1:1). The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The resulting residue was washed with hexane to give the titled compound (480 mg).
- 20
- 25 Melting point: 305 - 307°C.

Reference Example 45

4-(2-Benzo[b]furanyl)benzoic acid



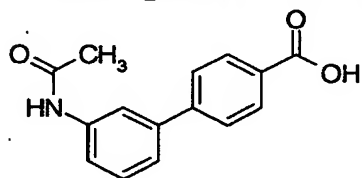
- 30 Benzofuranyl-2-boric acid (2.1 g), palladium tetratriphenylphosphine (200 mg) and 2M aqueous sodium

carbonate solution were added to toluene (40 ml) - ethanol (10 ml) solution of ethyl 4-bromobenzoate (2.3 g), which was refluxed at 80°C for 5 hours under an argon atmosphere.

The reaction mixture was diluted with water, and
5 extraction was conducted using ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The resulting residue was purified using silica gel
10 chromatography (development solvent; ethyl acetate:hexane = 1:4), and concentrated, which was dissolved in methanol (10 ml) - THF (10 ml). 8 mol of aqueous sodium hydroxide solution (8 ml) was added to the resulting solution at room temperature, which was stirred for 2 hours. After 1 mol of hydrochloric acid was added to the reaction mixture to
15 make the mixture acidic, extraction was conducted using ethyl acetate-THF (1:1). The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The resulting residue was washed with hexane to give the titled compound (2.272 g).
20 Melting point: 292 - 294°C.

Reference Example 46

3'-Acetylamino-4-biphenylcarboxylic acid

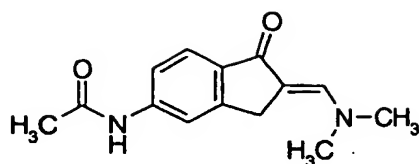


25 The titled compound was produced in the same manner as in Reference Example 45.

Melting point: 300 - 301°C

Reference Example 47

30 N-[2-[(E)-(Dimethylamino)methyldene]-1-oxo-2,3-dihydro-1H-inden-5-yl]acetamide

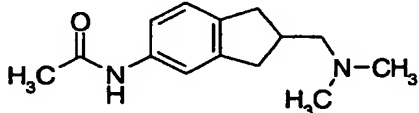


Dimethylformamide dimethylacetal was added to 5-acetamido-1-indanone (2.5 g, 13.2 mmol), which was stirred at 100°C for 3.5 hours, and cooled to room temperature. The precipitated crude products were collected, which was washed with ethyl acetate to give the titled compound (2.73 g).

¹H NMR (DMSO-d₆) δ: 2.08 (3H, s), 3.13 (6H, s), 3.87 (2H, s), 7.31 (1H, s), 7.52 (2H, m), 7.86 (1H, s), 10.16 (1H, s).

Reference Example 48

N-[2-[(Dimethylamino)methyl]-2,3-dihydro-1H-inden-5-yl]acetamide



N-[2-[(E)-(Dimethylamino)methylidene]-1-oxo-2,3-dihydro-1H-inden-5-yl]acetamide (2.70 g, 12.3 mmol) obtained in Reference Example 47 and 10% palladium-carbon (0.3 g) were added to a mixed solution of methanol (60 ml) and acetic acid (6 ml), which was stirred at 40°C under a hydrogen atmosphere for 1 day. After the catalyst was filtered, the filtrate was distilled out under reduced pressure. 1N hydrochloric acid (15 ml) was added to the reaction mixture, which was washed with ethyl acetate.

Then, potassium carbonate was added to the mixture, and extraction was conducted using ethyl acetate. The extract was washed with saturated aqueous sodium chloride solution, dried using anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The resulting residue was purified using aluminum column chromatography (development solvent: ethyl acetate) to give the titled

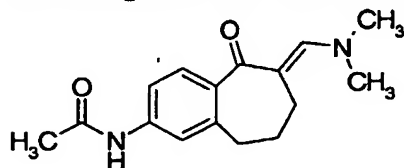
compound.

^1H NMR (CDCl_3) δ : 2.15 (3H, s), 2.25 (6H, s), 2.28 (2H, m), 2.61 (3H, m), 3.02 (2H, m), 7.11 (2H, m), 7.26 (1H, s), 7.39 (1H, s).

5

Reference Example 49

N-[6-[(E)-(Dimethylamino)methylidene]-5-oxo-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-2-yl]acetamide



10

The titled compound was obtained by carrying out the same operation as in Reference Example 47, using N-(5-oxo-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-2-yl)acetamide.

^1H -NMR (CDCl_3) δ : 1.78-1.90 (2H, m), 2.17 (3H, s), 2.34 (2H, t, J = 6.6 Hz), 2.74 (2H, t, J = 6.8 Hz), 3.11 (6H, s), 7.21 (1H, d, J = 8.1 Hz), 7.48-7.63 (3H, m), 7.73 (1H, s).

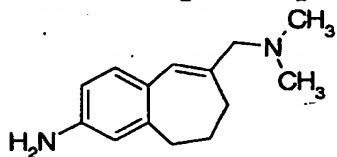
15

Melting point: 177 - 180°C (crystallization solvent: ethyl acetate-diethyl ether)

20

Reference Example 50

8-[(Dimethylamino)methyl]-6,7-dihydro-5H-benzo[a]cyclohepten-3-amine



The titled compound was obtained as an oily substance by carrying out the same operation as in Example 41-2), using N-[6-[(E)-(dimethylamino)methylidene]-5-oxo-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-2-yl]acetamide obtained in Reference Example 49.

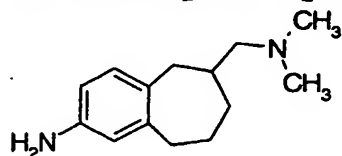
^1H -NMR (CDCl_3) δ : 1.90-2.01 (2H, m), 2.22 (6H, s), 2.35 (2H, t, J = 6.3 Hz), 2.72 (2H, t, J = 5.4 Hz), 2.91 (2H, s), 3.7

30

(2H, br, NH₂), 6.28 (1H, s), 6.40-6.50 (2H, m), 6.94 (1H, d, J = 7.8 Hz).

Reference Example 51

- 5 6-[(Dimethylamino)methyl]-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-2-amine



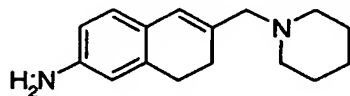
- The titled compound was obtained as an oily substance, by carrying out the same operation as in Reference Example 48, using 8-[(dimethylamino)methyl]-6,7-dihydro-5H-benzo[a]cyclohepten-3-amine.

¹H-NMR (CDCl₃) δ: 1.30-1.63 (3H, m), 1.65-2.22 (10H, m), 2.44-2.80 (4H, m), 3.5 (2H, br, NH₂), 6.35-6.48 (2H, m), 6.92 (1H, d, J = 7.8 Hz).

15

Reference Example 52

- 6-(1-Piperidinylmethyl)-7,8-dihydro-2-naphthalenamine



- 1) A mixture of 6-acetamido-2-(N,N-dimethylaminomethylidene)-1-tetralone (11 g) obtained in Example 41-1) and piperidine (100 ml) was refluxed with heating for 24 hours. After excess piperidine was distilled out under reduced pressure, the resulting residue was crystallized using tetrahydrofuran-isopropyl ether to give 6-acetamido-2-(1-piperidinylmethylidene)-1-tetralone (7 g) as a light yellow powder.

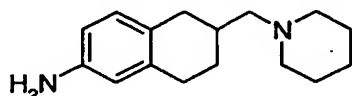
- 2) The titled compound was obtained as an amorphous powder by carrying out the same operations as in Example 41-2), using 6-acetamido-2-(1-piperidinylmethylidene)-1-tetralone obtained in above 1).

¹H NMR (CDCl₃) δ: 1.44-1.57 (6H, m), 2.25-2.34 (6H, m), 2.72 (2H, t, J=8.0 Hz), 2.98 (2H, s), 3.59 (2H, s), 6.23 (1H,

s), 6.45-6.47 (2H, m), 6.81 (1H, d, J=8.7 Hz).

Reference Example 53

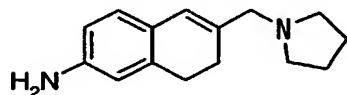
6-(1-Piperidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenamine



The titled compound was obtained as an amorphous powder by carrying out the same operations as in Reference Example 48, using 6-(1-piperidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 52.
¹H NMR (CDCl₃) δ: 1.25-2.82 (19H, m), 3.36 (2H, bs), 6.44-6.49 (2H, m), 6.88 (1H, d, J=8.1 Hz).

Reference Example 54

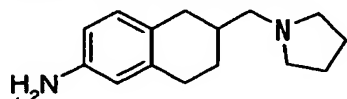
6-(1-Pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine



The titled compound was obtained as an amorphous powder by carrying out the same operations as in Reference Example 52, using 6-acetamido-2-(N,N-dimethylaminomethylidene)-1-tetralone obtained in Example 41-1).
¹H NMR (CDCl₃) δ: 1.76-1.80 (4H, m), 2.30 (2H, t, J = 7.8 Hz), 2.47-2.49 (4H, m), 2.74 (2H, t, J = 7.8 Hz), 3.13 (2H, s), 3.59 (2H, brs), 6.26 (1H, s), 6.45-6.47 (2H, m), 6.82 (1H, d, J = 8.6Hz).

Reference Example 55

6-(1-Pyrrolidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenamine



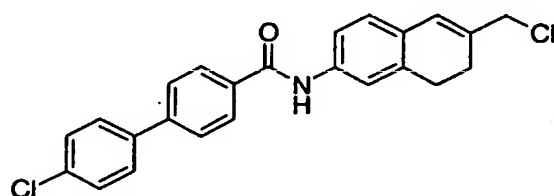
The titled compound was obtained as an amorphous

powder by carrying out the same operations as in Reference Example 48, using 6-(1-pyrrolidinymethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

¹H NMR (CDCl₃) δ : 1.45-1.90 (1H, m), 1.55-2.80 (16H, m),
5 3.48 (2H, brs), 6.44 (1H, s), 6.47 (2H, d, J = 8.1 Hz),
6.88 (2H, d, J = 8.1 Hz).

Reference Example 56

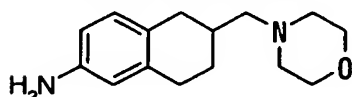
4'-Chloro-N-[6-(chloromethyl)-7,8-dihydro-2-naphthalenyl] [1,1'-biphenyl]-4-carboxamide
10



After 1-chloroethyl chloroformate (0.23 ml) was added to tetrahydrofuran solution (30 ml) of 4'-chloro-N-[6-(dimethylamino)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide (750 mg) at
15 -78°C, the temperature of the solution was raised to room temperature over 30 minutes. The solvent was distilled out under reduced pressure. The resulting residue was crystallized using tetrahydrofuran-n-hexane to give the
20 titled compound (600 mg).
Melting point: 179 - 181°C (crystallization solvent: tetrahydrofuran-n-hexane)

Reference Example 57

6-(4-Morpholinymethyl)-5,6,7,8-tetrahydro-2-naphthalenamine
25



The titled compound was obtained as an amorphous powder by carrying out, in order, the same operations as
30 in Reference Example 52 and Reference Example 48, using 6-acetamido-2-(N,N-dimethylaminomethylidene)-1-

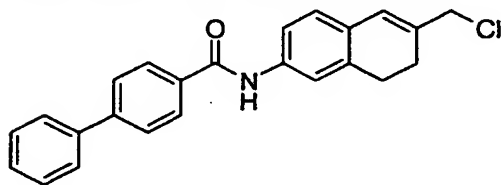
tetralone obtained in Example 41-1).

¹H NMR (CDCl₃) δ: 1.22-1.41 (1H, m), 1.80-1.82 (2H, m), 2.22-2.34 (10H, m), 3.50 (2H, s), 3.69-3.72 (1H, m), 6.40 (1H, s), 6.44 (1H, d, J = 8.1 Hz), 6.85 (1H, d, J = 8.1 Hz).

5

Reference Example 58

N-[6-(Chloromethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



10

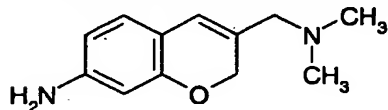
The titled compound was obtained by carrying out the same operations as in Reference Example 56, using N-[6-[(dimethylamino)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide obtained in Example 47.

15

Melting point: 163 - 165°C (crystallization solvent: tetrahydrofuran-n-hexane)

Reference Example 59

3-[(N,N-Dimethylamino)methyl]-2H-chromen-7-amine



20

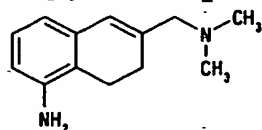
The titled compound was obtained by carrying out, in order, the same operations as in Examples 41-1) and 41-2), using 7-acetylamino-3,4-dihydrochromen-4-on.

¹H-NMR (CDCl₃) δ: 2.20 (6H, s), 2.94 (2H, s), 3.66 (2H, brs), 4.71 (2H, s), 6.16-6.21 (2H, m), 6.76 (1H, d, J = 7.8 Hz).

25

Reference Example 60

6-[(Dimethylamino)methyl]-7,8-dihydro-1-naphthalenamine



1) Methyl 4-(2-aminophenyl)butanoate hydrochloride (7.20 g, 0.037 mol) synthesized by a known method by documents (Synthetic communications, 26(18), 3443 (1996)) and triethylamine (5.06 g, 0.05 mol) were dissolved in tetrahydrofuran (60ml). Acetyl chloride (3.51 g, 0.045 mol) was added dropwise to the mixture, which was stirred at room temperature for 30 minutes. Ethyl acetate and 1N hydrochloric acid were added to the reaction mixture, and extraction was conducted. The organic layer was washed with water, concentrated and dried. A mixed solution of ethyl acetate - n-hexane (1 : 1) was added to the residue.

The crystallized product was collected by filtration, to give methyl 4-(2-acetylamino-phenyl)butanoate (6.40g) as a white powder.

¹H-NMR (CDCl₃) δ : 1.77-1.86 (2H, m), 2.29 (3H, s), 2.41-2.45 (2H, m), 2.59-2.62 (2H, m), 3.74 (3H, s), 7.03 (1H, t, J=7.3 Hz), 7.11-7.12 (1H, m), 7.22 (1H, t, J=7.3 Hz), 8.08 (1H, d, J=8.1 Hz), 8.33 (1H, s).

2) Polyphosphoric acid (100g) was heated at 130°C, then methyl 4-(2-acetylamino-phenyl)butanoate (6.40g, 0.027mol) obtained in 1) was added under stirring. After stirring for 1 hour, the reaction mixture was poured into ice water, and ethyl acetate and water were added, then extraction was conducted by adding water. The organic layer was washed with saturated sodium hydrogen carbonate solution and aqueous sodium chloride solution, and concentrated. A mixed solution of ethyl acetate - n-hexane (1:1) was added to the residue, and the crystallized product was collected by filtration, to give 5-acetylamino-1-tetralone (2.80g) as a white powder.

¹H-NMR (CDCl₃) δ : 2.10-2.19 (2H, m), 2.24 (3H, s), 2.66 (2H, t, J=6.3 Hz), 2.84 (2H, t, J=5.7 Hz), 7.06 (1H, brs), 7.34 (1H, t, J=7.5 Hz), 7.82 (1H, d, J=7.5 Hz), 7.95 (1H, d, J=7.5 Hz).

3) 5-Acetylamino-1-tetralone (0.6g, 3.0 mmol) obtained was dissolved in dimethylformamide dimethylacetal

(20ml), which was refluxed with heating for 4 hours. The crystallized product was collected by filtration, which was washed with ethyl acetate, to give 5-acetylamino-2-(dimethylamino)methylidene-1-tetralone (0.58g) as a yellow powder.

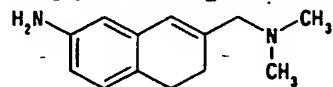
$^1\text{H-NMR}$ (CDCl_3) δ : 2.21 (3H, s), 2.68-2.72 (2H, m), 2.86-2.90 (2H, m), 3.11 (6H, s), 7.26-7.31 (2H, m), 7.62 (1H, m), 7.69 (1H, s), 7.92 (1H, m).

4) Sodium triacetoxhydroborate (424 mg, 2.0 mmol) was dissolved in a mixed solution of ethyl acetate (5ml) and tetrahydrofuran (1ml) under ice-cooling. 5-Acetylamino-2-dimethylaminomethylidene-1-tetralone (129 mg, 0.5 mmol) obtained in 3) was added to the mixture, which was stirred for 15 minutes. The reaction mixture was concentrated, and methanol (10ml) was added to the residue, and sodium borohydride (38 mg, 1 mmol) was added under ice-cooling. After stirring for 1 hour, the reaction mixture was concentrated. 5N Hydrochloric acid and ethyl acetate were added to the residue, and extraction was conducted. The water layer was refluxed with heating for 2 hours. 4N sodium hydroxide solution and ethyl acetate were added to the reaction mixture, and extraction was conducted. The organic layer was washed with water, and concentrated. The residue was purified by alumina column chromatography (development solvent; ethyl acetate : n-hexane=1:1), to give the titled compound (80 mg) as a colorless oily substance.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.24(6H, s), 2.37(2H, t, $J=8.1$ Hz), 2.63(2H, t, $J=8.1$ Hz), 2.97(2H, s), 3.58(2H, brs), 6.29(1H, s), 6.53(1H, d, $J=8.1$ Hz), 6.57 (1H, d, $J=8.1$ Hz), 6.97(1H, t, $J=8.1$ Hz).

Reference Example 61

7-[(Dimethylamino)methyl]-5,6-dihydro-2-naphthalenamine



1) 7-Nitro-1-tetralone (8.32 g, 0.044 mol) and concentrated hydrochloric acid (24 ml, 0.29 mol) were dissolved in methanol (100 ml), and an iron powder (7.30 g, 0.13 mol) was gradually added over 1 hour. After
5 stirring for 1 hour, the reaction mixture was concentrated.

4N Sodium hydroxide solution and ethyl acetate were added to the residue, and extraction was conducted. The organic layer was dried, and concentrated. Tetrahydrofuran (100 ml) and triethylamine (5.05 g, 0.05 mol) was added to the
10 residue. Further, acetyl chloride (3.92 g, 0.05 mol) was added under ice-cooling. After stirring for 30 minutes, ethyl acetate and 1N hydrochloric acid were added, and extraction was conducted. The organic layer was concentrated, and the residue was purified with silica gel
15 column chromatography (development solvent: ethyl acetate), to give 7-acetylamino-1-tetralone (7.52 g) as a white powder.

¹H-NMR (CDCl₃) δ: 2.09-2.18 (2H, m), 2.21 (3H, s), 2.65 (2H, t, J=6.3 Hz), 2.94 (2H, t, J=6.3 Hz), 7.24 (1H, d, J=8.4
20 Hz), 7.82 (1H, s), 7.98 (1H, brs), 8.15 (1H, d, J=7.5 Hz).

2) 7-Acetylamino-2-[(dimethylamino)methylidene]-1-tetralone (2.95 g) was obtained as a white powder by the same method as in Reference Example 60-3), using 7-acetylamino-1-tetralone (3.00 g, 0.0148 mol) obtained in
25 1).

¹H-NMR (CDCl₃) δ: 2.17 (3H, s), 2.78-2.82 (2H, m), 2.88-2.93 (2H, m), 3.14 (6H, s), 7.14 (1H, d, J=8.1 Hz), 7.74 (1H, s), 7.76 (1H, s), 8.09-8.12 (1H, m), 8.24 (1H, s).

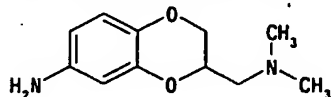
3) The titled compound (300 mg) was obtained as a colorless oily substance by the same method as in Reference Example 60-4), using 7-acetylamino-2-[(dimethylamino)methylidene]-1-tetralone (628 mg, 2.43
30 mmol) obtained in 2).

¹H-NMR (CDCl₃) δ: 2.23 (6H, s), 2.29 (2H, t, J=8.4 Hz), 2.71 (2H, t, J=8.4 Hz), 2.97 (2H, s), 3.52 (2H, brs), 6.24 (1H, s), 6.41 (1H, s), 6.46 (1H, d, J=7.8 Hz), 6.90 (1H, d,

J=7.8 Hz).

Reference Example 62

N,N-Dimethyl-N-[(7-amino-2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amine



1) 1,2-Dihydroxy-4-nitrobenzene (5.00 g, 0.032 mol), potassium carbonate (9.67 g, 0.07 mol) and epibromohydrin (5.30 g, 0.039 mol) were dissolved in dimethylformamide (100ml), which was stirred at 100°C for 1 hour. Water was added to the reaction mixture, and extraction was conducted using ethyl acetate. The organic layer was washed with water, and concentrated. The residue was purified by alumina column chromatography (development solvent : ethyl acetate). The eluent was washed with a mixed solution of ethyl acetate - n-hexane (1:1), to give (7-nitro-2,3-dihydro-1,4-benzodioxin-2-yl)methanol (3.31 g) as a white powder.

¹H-NMR (CDCl₃) δ : 1.95-1.99 (1H, m), 3.89-3.97 (2H, m), 4.19-4.29 (2H, m), 4.41-4.45 (1H, m), 6.96 (1H, d, J=8.6 Hz), 7.78-7.81 (2H, m).

2) (7-Nitro-2,3-dihydro-1,4-benzodioxin-2-yl)methanol (1.00 g, 4.74 mmol) obtained in 1) and triethylamine (719 mg, 7.10 mmol) were dissolved in dimethylformamide (30 ml), and methanesulfonyl chloride (651 mg, 5.68 mmol) was added, which was stirred at room temperature for 30 minutes. Then, an aqueous dimethylamine solution was added and stirred at 60°C for 5 hours. Water was added to the reaction mixture, and extraction was conducted using ethyl acetate. The organic layer was washed with water, and concentrated. The residue was purified by alumina column chromatography (development solvent ; ethyl acetate : n-hexane = 3:7), to give N,N-dimethyl-N-[(7-nitro-2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amine (802 mg) as a colorless oily substance.

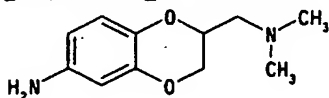
¹H-NMR (CDCl₃) δ : 2.34 (6H, s), 2.50-2.68 (2H, m), 4.02-4.09 (2H, m), 4.30-4.36 (1H, m), 4.39-4.44 (2H, m), 6.94 (1H, d, J=8.9Hz), 7.76-7.84 (2H, m).

3) N,N-Dimethyl-N-[(7-nitro-2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amine (802 mg, 3.37 mmol) obtained in 2) and concentrated hydrochloric acid (3 ml) was dissolved in methanol (10 ml), and an iron powder (0.80 g, 14 mmol) was quietly added over 1 hour. After stirring for 1 hour, the reaction mixture was concentrated. 4N Sodium hydroxide solution and ethyl acetate were added to the residue, and extraction was conducted. The organic layer was dried, and concentrated. The residue was purified by silica gel column chromatography (development solvent: ethyl acetate - n-hexane = 3:7), to give the titled compound (514 mg) as a colorless oily substance.

¹H-NMR (CDCl₃) δ : 2.32 (6H, s), 2.43-2.64 (2H, m), 3.40 (2H, s), 3.86-3.93 (1H, m), 4.19-4.27 (2H, m), 6.18-6.22 (1H, m), 6.29 (1H, s), 6.67 (1H, d, J=8.7 Hz).

20 Reference Example 63

N,N-Dimethyl-N-[(6-amino-2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amine



1) 1,2-Dihydroxy-4-nitrobenzene (4.65 g, 0.030 mol), potassium carbonate (8.71 g, 0.063 mol) and methoxymethyl chloride (2.42 g, 0.030 mol) were dissolved in dimethylformamide (50 ml), which was stirred at 40°C for 30 minutes. Epibromohydrin (7.20 g, 0.045 mol) was added to the mixture, which was stirred at 60°C for 80 minutes.

Then water was added, and extraction was conducted using ethyl acetate. The organic layer was washed with water, and concentrated. The residue was purified by alumina column chromatography (development solvent: ethyl acetate - n-hexane = 1:4), to give 2-[[2-(methoxymethoxy)-5-nitrophenoxy]methyl]oxirane (2.61 g) as a white powder.

¹H-NMR (CDCl₃) δ: 2.79-2.81 (1H, m), 2.93-2.96 (1H, m), 3.41 (1H, m), 3.53 (3H, s), 4.01-4.07 (1H, m), 4.40-4.45 (1H, m), 5.32 (2H, s), 7.22 (1H, d, J=9.0 Hz), 7.82-7.91 (2H, m).

5 2) 2-[[2-(Methoxymethoxy)-5-nitrophenoxy]methyl]oxirane (4.00 g, 0.016 mol) obtained in 1) was dissolved in methanol (50 ml), and 10% hydrochloric acid-methanol solution (10 ml) was added, which was stirred at room temperature for 30 minutes. The
10 solvent was concentrated, and methanol (30 ml) and potassium carbonate (6.50 g, 0.047 mol) were added to the residue, which was stirred at 60°C for 1 hour. The solvent was concentrated, water was added, and extraction was conducted using ethyl acetate. The organic layer was
15 washed with water, and concentrated. The residue was purified by alumina column chromatography (development solvent: ethyl acetate), to give (6-nitro-2,3-dihydro-1,4-benzodioxin-2-yl)methanol (2.12 g) as a white powder.
¹H-NMR (CDCl₃) δ: 1.90-1.94 (1H, m), 3.89-3.97 (2H, m),
20 4.19-4.28 (2H, m), 4.41-4.45 (1H, m), 6.97 (1H, d, J=8.6 Hz), 7.78-7.82 (2H, m).

 3) N,N-Dimethyl-N-[(6-nitro-2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amine (910 mg) was obtained as a colorless oily substance, by the same method as in Reference
25 Example 62-2), using (6-nitro-2,3-dihydro-1,4-benzodioxin-2-yl)methanol (1.00 g, 4.74 mmol) obtained in 2).

¹H-NMR (CDCl₃) δ: 2.35 (6H, s), 2.52-2.70 (2H, m), 3.98-4.05 (2H, m), 4.35-4.39 (3H, m), 6.95-6.98 (1H, m), 7.77-7.80
30 (2H, m).

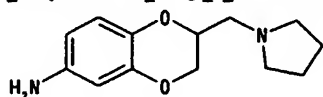
 4) The titled compound (750 mg) was obtained as a colorless oily substance, by the same method as in Reference Example 62-3), using N,N-dimethyl-N-[(6-nitro-2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amine (910 mg, 3.82
35 mmol) obtained in 3).

¹H-NMR (CDCl₃) δ: 2.32 (6H, s), 2.43-2.64 (2H, m), 3.40 (2H,

s), 3.86-3.92 (1H, m), 4.13-4.27 (2H, m), 6.19-6.28 (2H, m), 6.67-6.70 (1H, m).

Reference Example 64

- 5 1-[(6-Amino-2,3-dihydro-1,4-benzodioxin-2-yl)methyl]pyrrolidine

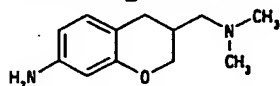


- 1) 1-[(6-Nitro-2,3-dihydro-1,4-benzodioxin-2-yl)methyl]pyrrolidine (1.30 g) was obtained as a colorless oily substance, by the same method as in Reference Example 62-2), using (6-nitro-2,3-dihydro-1,4-benzodioxin-2-yl)methanol (1.12 g, 5.30 mmol) and pyrrolidine (10 ml).
10 ¹H-NMR (CDCl₃) δ: 1.79-1.83 (4H, m), 2.60-2.62 (4H, m), 2.78 (2H, d, J=5.9 Hz), 4.00-4.07 (1H, m), 4.38-4.42 (2H, m),
15 6.95-6.98 (1H, m), 7.76-7.80 (2H, m).

- 2) The titled compound (1.03 g) was obtained as a colorless oily substance, by the same method as in Reference Example 62-3), using 1-[(6-nitro-2,3-dihydro-1,4-benzodioxin-2-yl)methyl]pyrrolidine (1.30 g, 4.92 mmol).
20 ¹H-NMR (CDCl₃) δ: 1.74-1.83 (4H, m), 2.54-2.63 (4H, m), 2.69-2.72 (2H, m), 3.40 (2H, s), 3.91-3.97 (1H, m), 4.18-4.30 (2H, m), 6.18-6.25 (2H, m), 6.70 (1H, d, J=8.4 Hz).

- 25 Reference Example 65

N-[(7-Amino-3,4-dihydro-2H-chromen-3-yl)methyl]-N,N-dimethylamine



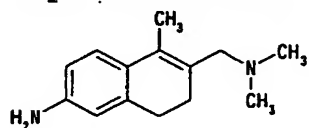
- 3-[(N,N-Dimethylamino)methyl]-2H-chromen-7-amine
30 (150 mg, 0.73 mmol) obtained in Reference Example 59, 1N hydrochloric acid (0.5 ml) and 10% palladium carbon (40 mg) was dissolved in methanol (5 ml), and catalytic hydrogenation was conducted under normal temperature and normal pressure. After a catalyst was filtered out, the

filtrate was concentrated, and the residue was purified by alumina column chromatography (development solvent; ethyl acetate : n-hexane = 3:7), to give the titled compound (15 mg) as a colorless oily substance.

- 5 $^1\text{H-NMR}$ (CDCl_3) δ : 2.20-2.24 (3H, m), 2.24 (6H, m), 2.30-2.40 (1H, m), 2.75-2.80 (1H, m), 3.60 (1H, m), 3.75-3.80 (2H, m), 4.20-4.25 (1H, m), 6.20 (1H, m), 6.21-6.25 (1H, m), 6.82 (1H, d, $J=7.8$ Hz).

10 Reference Example 66

6-[(Dimethylamino)methyl]-5-methyl-7,8-dihydro-2-naphthalenamine



- 15 1) 6-Acetylamino-1-tetralone (5.5 g, 0.027 mol) and dimethylmethylenammonium chloride (6.3 g, 0.068 mol) were dissolved in a mixed solution of acetonitrile (100 ml) and tetrahydrofuran (100 ml), which was stirred for 48 hours.

The crystallized product was collected by filtration, washed with tetrahydrofuran, and dissolved in ethyl acetate. 0.5N Sodium hydroxide solution was added to the solution for liquid separation. The organic layer was concentrated, to give 6-acetylamino-2-[(dimethylamino)methyl]-1-tetralone (4.48 g) as a colorless oily substance.

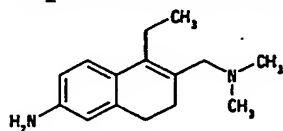
- 25 2) 6-Acetylamino-2-[(dimethylamino)methyl]-1-tetralone (260 mg, 1.00 mmol) obtained was dissolved in tetrahydrofuran (10 ml). 1M Methyl magnesium bromide - tetrahydrofuran solution (3 ml) (3.00 mmol) was added to the solution under ice-cooling, which was stirred at room temperature for 16 hours. Aqueous ammonium chloride solution was added to the reaction mixture, and extraction was conducted using ethyl acetate. The organic layer was concentrated, and 5N hydrochloric acid and ethyl acetate were added to the residue for liquid separation.

Concentrated hydrochloric acid was added to the water layer, which was refluxed for 4 hours. The reaction mixture was concentrated, and 1N sodium hydroxide solution and ethyl acetate were added to the residue and extraction was conducted. The organic layer was concentrated, and the residue was purified by alumina column chromatography (development solvent; ethyl acetate : n-hexane = 3:7), to give the titled compound (83 mg) as a colorless oily substance.

¹H-NMR (CDCl₃) δ : 2.04 (3H, s), 2.24 (6H, s), 2.28 (2H, t, J=7.4 Hz), 2.66 (2H, t, J=7.4 Hz), 3.04 (2H, s), 3.62 (2H, s), 6.49 (1H, s), 6.51-6.55 (1H, m), 7.10 (1H, d, J=8.1 Hz).

Reference Example 67

6-[(Dimethylamino)methyl]-5-ethyl-7,8-dihydro-2-naphthalenamine

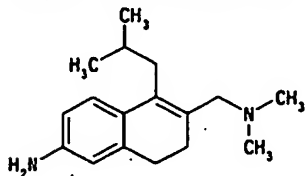


The titled compound was obtained as a colorless oily substance by the same manner as in Reference Example 66-2), using 6-acetylamino-2-(dimethylamino)methyl-1-tetralone obtained in Reference Example 66-1) and ethyl magnesium bromide.

¹H-NMR (CDCl₃) δ : 1.06 (3H, t, J=7.5 Hz), 2.24 (6H, s), 2.27 (2H, m), 2.52-2.66 (4H, m), 3.04 (2H, s), 3.61 (2H, s), 6.51 (1H, s), 6.51-6.55 (1H, m), 7.11 (1H, d, J=8.1 Hz).

Reference Example 68

6-[(Dimethylamino)methyl]-5-isobutyl-7,8-dihydro-2-naphthalenamine

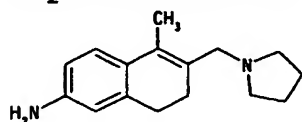


The titled compound was obtained as a colorless oily substance by the same manner as in Reference Example 66-2), using 6-acetylamino-2-[(dimethylamino)methyl]-1-tetralone obtained in Reference Example 66-1) and isobutyl magnesium bromide.

¹H-NMR (CDCl₃) δ: 0.88 (6H, d, J=6.7 Hz), 1.73-1.79 (1H, m), 2.21 (6H, s), 2.28 (2H, t, J=7.0 Hz), 2.44 (2H, d, J=7.3 Hz), 2.63 (2H, t, J=7.0 Hz), 3.09 (2H, s), 3.60 (2H, s), 6.49 (1H, s), 6.51-6.53 (1H, m), 7.08 (1H, d, J=7.8 Hz).

Reference Example 69

5-Methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine



1) 6-Acetylamino-2-[(dimethylamino)methylidene]-1-tetralone (4.90 g, 0.017 mol) obtained in Example 41-1) was suspended in pyrrolidine (25 ml), which was refluxed with heating for 2 hours. The crystallized product was collected by filtration, washed with a mixed solution of ethyl acetate and n-hexane (1:1), to give 6-acetylamino-2-(1-pyrrolidinylmethylidene)-1-tetralone (5.03 g) as yellow crystals.

¹H-NMR (CDCl₃) δ: 1.75-2.00 (4H, m), 2.19 (3H, s), 2.70-3.00 (4H, m), 3.50-3.70 (4H, m), 7.20-7.25 (1H, m), 7.67 (1H, s), 7.70-7.90 (2H, m), 7.97 (1H, d, J=8.4 Hz).

2) Sodium triacetoxyhydroborate (3.18 g, 0.015 mol) was dissolved in a mixed solution of ethyl acetate (50 ml) and tetrahydrofuran (12.5 ml) under ice-cooling, and 6-acetylamino-2-(1-pyrrolidinylmethylidene)-1-tetralone (2.84 g, 0.01 mol) obtained in 1) was added. After stirring for 1 hour, the reaction mixture was concentrated. 1N Sodium hydroxide solution and ethyl acetate were added to the residue, which was stirred. The crystallized product was collected by filtration, washed with a mixed solution

of ethyl acetate and n-hexane (1:1), to give 6-acetylamino-2-(1-pyrrolidinylmethyl)-1-tetralone (2.65 g) as a white powder.

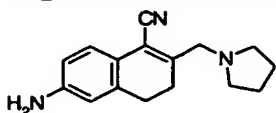
¹H-NMR (CDCl₃) δ: 1.78 (4H, m), 1.90-2.02 (1H, m), 2.20 (3H, s), 2.35-2.98 (10H, m), 7.20-7.23 (1H, m), 7.57 (1H, s), 7.66 (1H, m), 7.97 (1H, d, J=8.4 Hz).

3) The titled compound was obtained by the same manner as in Reference Example 66-2), using 6-acetylamino-2-(1-pyrrolidinylmethyl)-1-tetralone obtained in 2).

¹H-NMR (CDCl₃) δ: 1.73-1.79 (4H, m), 2.04 (3H, s), 2.31 (2H, t, J=7.4 Hz), 2.49-2.54 (4H, m), 2.65 (2H, t, J=7.8 Hz), 3.24 (2H, s), 3.60 (2H, brs), 6.48-6.54 (2H, m), 7.09 (1H, d, J=8.1 Hz).

Reference Example 70

6-Amino-2-(1-pyrrolidinylmethyl)-3,4-dihydro-1-naphthalenecarbonitrile



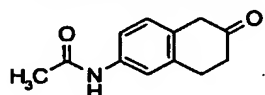
Trimethylsilylnitrile (1.02 ml, 7.68 mmol) and zinc iodide (22 mg, 0.0698 mmol) were added to dichloroethane solution (9 ml) of 6-acetylamino-2-(1-pyrrolidinylmethyl)-1-tetralone (1.00 g, 3.49 mmol) obtained in Reference Example 69-2), which was stirred at room temperature for 2 days. The solvent was distilled out under reduced pressure. Ethyl acetate was added to the obtained oily substance, which was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The resulting residue was purified by alumina column chromatography (development solvent; ethyl acetate), to give trimethylsilylcyanohydrin form (1.21 g) as an oily substance. 2.5N Hydrochloric acid was added to the oily substance (978 mg, 2.73 mmol), which was stirred at 100°C for 1.5 hours. The aqueous solution obtained was

washed with ethyl acetate. Potassium carbonate was added to the water layer to make it alkaline, and extraction was conducted using ethyl acetate. The extract was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and the solvent was distilled out under reduced pressure. The resulting oily substance was purified by alumina column chromatography (development solvent; hexane: ethyl acetate = 5:1), to give the titled compound (358 mg).

¹H NMR (CDCl₃) δ: 1.80 (4H, m), 2.56 (6H, m), 3.73 (2H, m), 3.50 (2H, s), 3.77 (2H, br), 6.46 (1H, s), 6.55 (1H, d, J = 8.1 Hz), 7.26 (1H, d, J = 8.1 Hz).

Reference Example 71

6-Acetamido-2-tetralone



1) Sodium borohydride (931 mg, 24.6 mmol) was added to a methanol solution (60 ml) of 6-acetamido-1-tetralone (5.00 g, 24.6 mmol) under ice-cooling, which was stirred at room temperature for 1 hour. Ethyl acetate was added to the reaction mixture, which was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then, the solvent was distilled out under reduced pressure. p-Toluenesulfonic acid (468 mg, 2.46 mmol) and toluene (120 ml) were added to the obtained alcohol form (5.05 g, 24.6 mmol), which was stirred at 100 °C for 1 hour. The solvent was distilled out under reduced pressure. Ethyl acetate was added to the residue, which was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The resulting oily substance was purified by silica gel column chromatography (development solvent; hexane:ethyl acetate = 1:1), and powdered with hexane to give N-(7,8-dihydro-2-naphthalenyl)acetamide (3.17 g).

¹H NMR (CDCl₃) δ : 2.16 (3H, s), 2.29 (2H, m), 2.28 (2H, m), 5.97 (1H, m), 6.42 (2H, d, J=9.6 Hz), 6.97 (1H, d, J=8.1 Hz), 7.14 (1H, br), 7.20 (1H, m), 7.32 (1H, s).

2) m-Chloroperbenzoic acid (5.13 g, 20.8 mmol) was added to a chloroform solution (80 ml) of N-(7,8-dihydro-2-naphthalenyl)acetamide (3.00 g, 16.0 mmol) obtained in 1) under ice-cooling, which was stirred at room temperature for 2 hours. Ethyl acetate was added to the reaction mixture, which was washed with saturated sodium hydrogencarbonate solution and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure.

The resulting oily substance was purified by alumina B column chromatography (development solvent; hexane : ethyl acetate = 1:1) . 1N Sodium hydroxide solution (10.7 ml) was added to a methanol solution (100 ml) of the obtained oily substance (3.20 g, 8.89 mmol) under ice-cooling, which was stirred at room temperature for 30 minutes. The solvent was distilled out under reduced pressure. Ethyl acetate was added to the residue, which was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The resulting oily substance was purified by alumina B column chromatography (development solvent; ethyl acetate : methanol = 10:1). p-

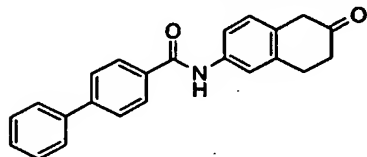
Toluenesulfonic acid (50mg, 0.262 mmol) and toluene (26 ml) were added to the obtained diol (596 mg, 2.62 mmol), which was stirred at 120°C for 3 hours. The solvent was distilled out under reduced pressure. Ethyl acetate was added to the residue, which was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure.

The resulting oily substance was purified by silica gel column chromatography (development solvent; hexane : ethyl acetate = 1:3), and powdered with diisopropyl ether, to give the titled compound (231 mg).

^1H NMR (CDCl_3) δ : 2.18 (3H, s), 2.54 (2H, m), 3.04 (2H, m), 3.76 (2H, s), 7.06 (1H, d, $J=8.1$ Hz), 7.21 (1H, dd, $J=8.1$, 2.0 Hz), 7.31 (1H, br), 7.61 (1H, d, $J=2.0$ Hz).

5 Reference Example 72

N-(6-Oxo-5,6,7,8-tetrahydro-2-naphthalenyl)[1,1'-biphenyl]-4-carboxamide



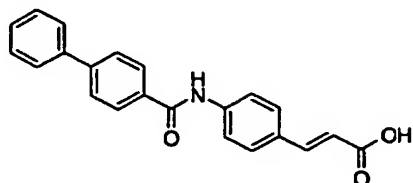
Concentrated hydrochloric acid (1.5 ml) was added to
10 6-acetamido-2-tetralone (20 mg, 0.098 mmol) obtained in
Reference Example 71, which was stirred at 100°C for 1 hour,
and the solvent was distilled out under reduced pressure.

Ethyl acetate was added to the residue, which was washed
with aqueous potassium carbonate solution and saturated
15 aqueous sodium chloride solution, dried over anhydrous
sodium sulfate, and then the solvent was distilled out under
reduced pressure. [1,1'-Biphenyl]-4-carbonyl chloride
(21.3 mg, 0.098 mmol) was added to a dimethylformamide
solution (0.5 ml) of the obtained oily substance and
20 triethylamine (0.014 ml, 0.098 mmol) under ice-cooling,
which was stirred at room temperature for 1 hour. Ethyl
acetate was added to the reaction mixture, which was washed
with 1N hydrochloric acid, aqueous potassium carbonate
solution and saturated aqueous sodium chloride solution,
25 dried over anhydrous sodium sulfate, and then the solvent
was distilled out under reduced pressure. The resulting
residue was purified by silica gel column chromatography
(development solvent; hexane:ethyl acetate = 1:1), to give
the titled compound (10 mg).

30 ^1H NMR (CDCl_3) δ : 2.56 (2H, t, $J=6.6$ Hz), 3.08 (2H, t, $J=6.6$
Hz), 3.57 (2H, s), 7.11 (1H, d, $J=8.1$ Hz), 7.43 (4H, m),
7.64 (2H, m), 7.72 (3H, m), 7.96 (3H, m).

Reference Example 73

(E)-3-[4-[[[1,1'-biphenyl]-4-ylcarbonyl)amino]phenyl]-2-propenic acid

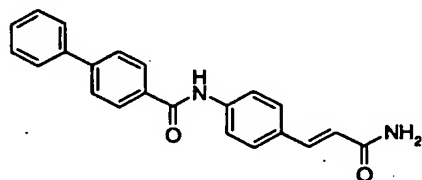


5 4-Phenylbenzoyl chloride (2.00 g, 9.23 mmol) was added to a mixed solution of 4-aminocinnamic acid (1.51 g, 9.23mmol) and sodium hydrogen carbonate (2.33 g, 27.7 mmol) in water and diethyl ether under ice-cooling, which was stirred for 5 hours. After the reaction mixture was
10 separated, 5N hydrochloric acid was added to water layer, and the precipitated crude product was washed with water and ethyl acetate, to give the titled compound (1.34 g). ¹H NMR (DMSO-d₆) δ: 6.84 (1H, d, J = 16.0 Hz), 7.43-7.93 (12H, m), 8.09 (2H, d, J = 8.4 Hz), 10.51 (1H, s).

15

Reference Example 74

N-[4-[(E)-3-Amino-3-oxo-1-propenyl]phenyl][1,1'-biphenyl]-4-carboxamide

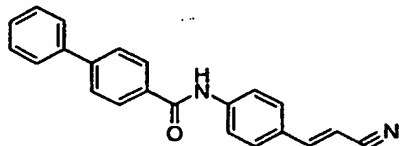


20 Chloro isobutylcarbonate (0.453 ml, 3.49 mmol) was added to a dimethylformamide suspension of (E)-3-[4-[[[1,1'-biphenyl]-4-ylcarbonyl)amino]phenyl]-2-propionic acid (1.00 g, 2.91 mmol) obtained in Reference Example 73 and triethylamine (0.527 ml, 3.79 mmol) under
25 ice-cooling, which was stirred for 30 minute. The solvent was distilled out under reduced pressure. Sodium hydrogencarbonate solution was added to the residue, and the precipitated crude product was washed with water and acetonitrile, to give the titled compound (936 mg).

¹H NMR (DMSO-d₆) δ: 6.56 (1H, d, J = 15.6 Hz), 7.05 (1H, br), 7.52 (7H, m), 7.86 (6H, m), 8.08 (2H, d, J = 7.6 Hz).

Reference Example 75

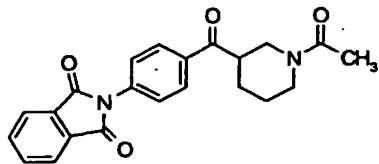
- 5 N-[4-[(E)-2-Cyanoethenyl]phenyl][1,1'-biphenyl]-4-carboxamide



- Cyanuric chloride (727 mg, 3.94 mmol) was added to a dimethylformamide suspension of (E)-3-[4-[[[1,1'-biphenyl]-4-ylcarbonyl)amino]phenyl]-2-propenic acid (900 mg, 2.63 mmol) obtained in Reference Example 74 at room temperature, which was stirred for 1 hour. After the solvent was distilled out under reduced pressure, the residue was dissolved in chloroform, which was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was stillled out under reduced pressure. The resulting residue was purified by silica gel column chromatography (development solvent; chloroform:ethyl acetate = 20:1), to give the titled compound (561 mg) as a colorless powder from diethyl ether.

¹H NMR (DMSO-d₆) δ: 6.37 (1H, d, J = 16.4 Hz), 7.43-7.51 (4H, m), 7.65-7.93 (8H, m), 8.08 (2H, d, J = 8.6 Hz).

- 25 Reference Example 76
2-[4-[(1-Acetyl-3-piperidinyl)carbonyl]phenyl]-1H-isoindol-1,3(2H)-dione



- 1) Thionyl chloride (2.12 ml, 32.1 mmol) was added to fluorobenzene solution (20 ml) of 1-acetyl-3-

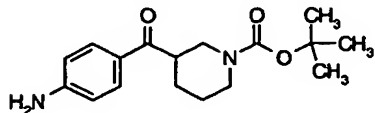
piperidinecarboxylic acid (5.00 g, 29.2 mmol) under ice-cooling, which was stirred at room temperature for 30 minutes. Aluminum chloride (9.74 g, 73.0 mmol) was added to the solution, which was stirred at 90°C for 1 hour. The reaction mixture was poured in ice, and extraction was conducted using ethyl acetate. The extract was washed with saturated aqueous sodium chloride solution, saturated sodium hydrogencarbonate solution, and again saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The resulting oily substance was purified by silica gel column chromatography (development solvent; hexane:ethyl acetate = 1:1), to give (1-acetyl-3-piperidinyl)(4-fluorophenyl)methanone (4.93 g).
¹H NMR (CDCl₃) δ: 1.61 (2H, m), 1.80 (2H, m), 2.11 and 2.15 (3H, s and s), 2.71 (1H, m), 3.11 and 3.42 (2H, m), 3.87 (1H, m), 4.53 and 4.83 (1H, m), 7.18 (2H, m), 8.02 (2H, m).

2) A dimethylformamide solution (50 ml) of (1-acetyl-3-piperidinyl)(4-fluorophenyl)methanone (4.92 g, 19.7 mmol) obtained in 1) and potassium phthalimide (3.66g, 19.7mmol) was stirred at 100°C for 12 hours under nitrogen atmosphere. The insoluble matters were filtered off, and the solvent was distilled out under reduced pressure. Ethyl acetate was added to the residue, which was washed with 1N hydrochloric acid and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The resulting oily substance was purified by silica gel column chromatography (development solvent; ethyl acetate), to give the titled compound (4.18 g) as a colorless powder from ethyl acetate - diisopropyl ether (1:5).

¹H NMR (CDCl₃) δ: 1.66 (2H, m), 1.86 (2H, m), 2.13 and 2.15 (3H, s and s), 2.74 (1H, m), 3.11 and 3.43 (2H, m), 3.88 (1H, m), 4.54 and 4.85 (1H, m), 7.66 (2H, m), 7.82 (2H, m), 7.99 (2H, m), 8.10 (2H, m).

Reference Example 77

tert-Butyl 3-(4-aminobenzoyl)-1-piperidinecarboxylate



5 1) Concentrated hydrochloric acid (53 ml) was added to 2-[4-[(1-acetyl-3-piperidiny)carbonyl]phenyl]-1H-isoindol-1,3(2H)-dione (4.00 g, 10.6 mmol) obtained in Reference Example 76, which was stirred at 100°C for 16 hours, and then insoluble matters were filtered off.

10 Potassium carbonate was added to the filtrate to make it alkaline, and extraction was conducted using ethyl acetate.

The extract was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure.

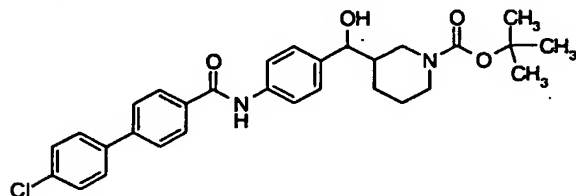
15 The resulting residue was powdered with diisopropyl ether, to give (4-aminophenyl)(3-piperidiny)methanone (1.69 g). ¹H NMR (CD₃OD) δ : 1.59-1.85 (4H, m), 2.68-2.72 (2H, m), 3.30 (2H, m), 3.45 (1H, m), 6.62 (2H, m), 7.74 (2H, m).

20 2) t-Butyl dicarbonate (0.562 ml, 2.45 mmol) was added to a tetrahydrofuran solution (12 ml) of (4-aminophenyl)(3-piperidiny)methanone (500 mg, 2.45 mmol) obtained in 1) under ice-cooling, which was stirred for 1.5 hours. Ethyl acetate was added to the reaction mixture, which was washed with saturated sodium hydrogencarbonate solution and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The resulting oily substance was purified by silica gel column chromatography (development solvent; hexane:ethyl acetate = 1:1), to give the titled compound (831 mg).

30 ¹H NMR (CDCl₃) δ 1.47 (9H, s), 1.47-1.52 (2H, m), 1.67-1.74 (2H, m), 2.00 (1H, m), 2.72 (1H, m), 2.90 (1H, m), 3.32 (1H, m), 4.13 (3H, m), 6.66 (2H, d, J=8.4Hz), 7.84 (2H, d, J=8.4Hz).

Reference Example 78

tert-Butyl 3-[[4-[[[(4'-chloro[1,1'-biphenyl]-4-yl)carbonyl]amino]phenyl](hydroxy)methyl]-1-piperidinecarboxylate

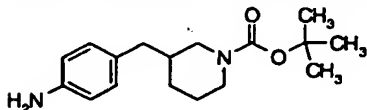


tert-Butyl 3-[4-[[[(4'-chloro[1,1'-biphenyl]-4-yl)carbonyl]amino]benzoyl]-1-piperidinecarboxylate (506 mg, 0.975 mmol) obtained in Example 127-1) was dissolved in a mixed solution of methanol and tetrahydrofuran (1:1) (10 ml). Sodium borohydride (73.8 mg, 1.95 mmol) was added to the solution under ice-cooling, which was stirred at room temperature for 1 hour. Ethyl acetate was added to the reaction mixture, which was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. Diisopropyl ether was added to the residue, to give the titled compound (488mg) as a colorless powder.

FABMS(pos) 521.2 [M+H]⁺

Reference Example 79

tert-Butyl 3-(4-aminobenzyl)-1-piperidinecarboxylate



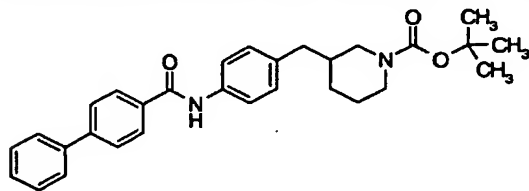
Sodium borohydride (433 mg, 11.5 mmol) was added to a methanol solution (25 ml) of tert-butyl 3-(4-aminobenzoyl)-1-piperidinecarboxylate (1.74g, 5.73mmol) obtained in Reference Example 77 under ice-cooling, which was stirred at room temperature for 1 hour. Ethyl acetate was added to the reaction mixture, which was washed with saturated aqueous sodium chloride solution, dried over

anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The resulting oily substance was purified by alumina B column chromatography (development solvent; ethyl acetate), to give an alcohol form. 1N hydrochloric acid (9.79 ml) and 10% palladium carbon (200 mg) were added to a methanol solution (300 ml) of the obtained alcohol form (1.00 g, 3.26 mmol), which was stirred for 16 hours under hydrogen atmosphere. The catalyst was filtered off, potassium carbonate was added to the filtrate to make it alkaline, and then the solvent was distilled out under reduced pressure. Ethyl acetate was added to the residue, which was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The resulting oily substance was purified by silica gel column chromatography (development solvent; hexane - ethyl acetate = 1:1), to give the titled compound (813 mg).

¹H NMR (CDCl₃) δ : 1.46-1.76 (14H, m), 2.25-2.80 (2H, m), 3.14 (2H, m), 3.76 (4H, m), 6.64 (2H, m), 7.01 (2H, m).

Reference Example 80

tert-Butyl 3-[4-[[[1,1'-biphenyl]-4-ylcarbonyl)amino]benzyl]-1-piperidinecarboxylate



The titled compound was obtained by carrying out the same operation as in Example 1, using tert-butyl 3-(4-aminobenzyl)-1-piperidinecarboxylate obtained in Reference Example 79 and [1,1'-biphenyl]-4-carboxylic acid.

Elemental analysis for C₃₀H₃₄N₂O₃ · 0.5H₂O

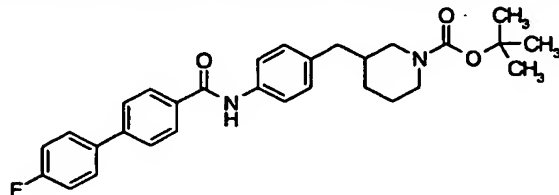
Calcd.: C, 75.13; H, 7.36; N, 5.84.

Found: C, 74.83; H, 7.25; N, 5.65.

Melting point: 135 - 137°C

Reference Example 81

- 5 tert-Butyl 3-[4-[[[(4'-fluoro[1,1'-biphenyl]-4-yl)carbonyl]amino]benzyl]-1-piperidinecarboxylate



- The titled compound was obtained by carrying out the same operation as in Example 1, using tert-butyl 3-(4-aminobenzyl)-1-piperidinecarboxylate obtained in Reference Example 80 and 4'-fluoro[1,1'-biphenyl]-4-carboxylic acid.

Elemental analysis for $C_{30}H_{33}FN_2O_3 \cdot 0.5H_2O$

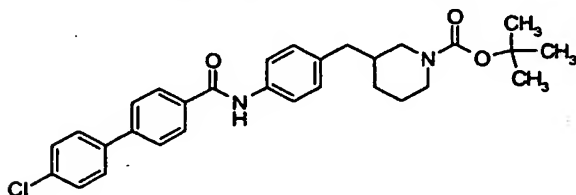
Calcd.: C, 72.41; H, 6.89; N, 5.63.

- 15 Found: C, 72.30; H, 7.07; N, 5.60.

Melting point: 138 - 141°C

Reference Example 82

- 20 tert-Butyl 3-[4-[[[(4'-chloro[1,1'-biphenyl]-4-yl)carbonyl]amino]benzyl]-1-piperidinecarboxylate



- The titled compound was obtained by carrying out the same operation as in Example 1, using tert-butyl 3-(4-aminobenzyl)-1-piperidinecarboxylate obtained in Reference Example 80 and 4'-chloro[1,1'-biphenyl]-4-carboxylic acid.

Elemental analysis for $C_{30}H_{33}ClN_2O_3 \cdot 0.5H_2O$

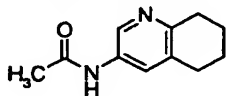
Calcd.: C, 70.09; H, 6.67; N, 5.45.

Found: C, 70.29; H, 6.50; N, 5.38.

Melting point: 173 - 176°C

Reference Example 83

N-(5,6,7,8-Tetrahydro-3-quinoliny)acetamide



1) Fuming nitric acid (100 ml) was added dropwise to concentrated sulfuric acid solution (200 ml) of 1-methyl-2-pyridone (20.7 g, 190 mmol) at 100°C, which was stirred for 16 hours. The reaction mixture was poured in ice. The resulting precipitate was collected, which was washed with water, to give 1-methyl-3,5-dinitro-2(1H)-pyridinone (3.0 g).

¹H NMR (DMSO-d₆) δ: 3.68 (3H, s), 9.01 (1H, d, J=3.0 Hz), 9.61 (1H, d, J=3.0 Hz).

15 2) 1N Methanolic ammonia solution (300 ml) of 1-methyl-3,5-dinitro-2(1H)-pyridinone (3.00g, 15.1mmol) obtained in 1) and 1-morpholino-1-cyclohexene (3.88 ml, 22.6 mmol) was stirred at 70°C for 3 hours. The solvent was distilled out under reduced pressure. The resulting residue was purified by alumina column chromatography (development solvent; ethyl acetate), to give 3-nitro-5,6,7,8-tetrahydroquinoline (2.42 g) as a powder from methanol - water (1:4).

25 ¹H NMR (DMSO-d₆) δ: 1.87 (4H, m), 2.90 (4H, m), 8.15 (1H, s), 9.16 (1H, s).

3) 10% Palladium-carbon (200 mg) was added to a methanol solution (68 ml) of 3-nitro-5,6,7,8-tetrahydroquinoline (2.41 g, 13.5 mmol) obtained in 2), which was stirred under hydrogen atmosphere for 16 hours.

30 After a catalyst was filtered off, the solvent was distilled out under reduced pressure. The resulting residue was dissolved in pyridine (35 ml). Anhydrous ethyl acetate (1.91 ml, 20.3 mmol) was added to the solution, which was stirred at room temperature for 1 hour. After completion of the reaction, the solvent was distilled out

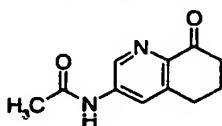
35

under reduced pressure. Diisopropyl ether - n-hexane (1:8) was added to the resulting residue, to give the titled compound (2.48 g) as a colorless powder.

¹H NMR (CDCl₃) δ: 1.80-1.87 (4H, m), 2.18 (3H, s), 2.77 (2H, m), 2.87 (2H, m), 7.72 (1H, br), 7.94 (1H, s), 8.24 (1H, s).

Reference Example 84

N-(8-Oxo-5,6,7,8-tetrahydro-3-quinolinyl)acetamide



10

1) m-Chloroperbenzoic acid (3.83 g, 15.5 mmol) was added to a chloroform solution (65 ml) of N-(5,6,7,8-tetrahydro-3-quinolinyl)acetamide (2.46 g, 12.9 mmol) obtained in Reference Example 83 under ice-cooling, which was stirred at room temperature for 16 hours. After the solvent was distilled out under reduced pressure, the residue was powdered with ethyl acetate, to give N-(1-oxide-5,6,7,8-tetrahydro-3-quinolinyl)acetamide (2.00 g).

20 ¹H NMR (DMSO-d₆) δ: 1.64 (2H, m), 1.75 (2H, m), 2.04 (3H, s), 2.66 (4H, m), 7.13 (1H, s), 8.56 (1H, s), 10.12 (1H, s).

2) Anhydrous ethyl acetate (30 ml) was added to N-(1-oxide-5,6,7,8-tetrahydro-3-quinolinyl)acetamide (1.99 g, 9.65 mmol) obtained in 1), which was stirred at 80°C for 3 hours. The reaction mixture was cooled to room temperature. The solvent was distilled out under reduced pressure, and the resulting residue was purified by alumina column chromatography (development solvent; ethyl acetate). The resulting oily substance was dissolved in methanol (110 ml). 1N Sodium hydroxide (21.5 ml) was added to the solution under ice-cooling, which was stirred at room temperature for 1 hour. The solvent was distilled out under reduced pressure. Chloroform was added to the residue,

30

which was washed with aqueous potassium carbonate solution and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The resulting
5 residue was purified by alumina column chromatography (development solvent; ethyl acetate:methanol = 5:1), to give N-(8-hydroxy-5,6,7,8-tetrahydro-3-quinolinyl)acetamide (1.08 g) as a powder from ethyl acetate and diisopropyl ether.

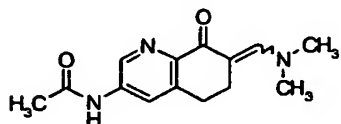
10 ^1H NMR (CDCl_3) δ : 1.79 (2H, m), 1.96 (1H, m), 2.22 (3H, s), 2.24 (1H, m), 2.82 (2H, m), 4.69 (1H, m), 7.49 (1H, br), 7.92 (1H, s), 8.30 (1H, s).

3) Manganese dioxide (4.47 g, 51.4 mmol) was added to chloroform (26 ml) solution of N-(8-hydroxy-5,6,7,8-tetrahydro-3-quinolinyl)acetamide (1.06 g, 5.14 mmol)
15 obtained in 2), which was stirred at room temperature for 1 day. After completion of the reaction, the insoluble matters were filtered off, and the filtrate was concentrated under reduced pressure. Diisopropyl ether and hexane were added to the resulting residue, to give the
20 titled compound (858 mg) as a colorless powder.

^1H NMR (CDCl_3) δ : 2.20 (2H, m), 2.26 (3H, s), 2.77 (2H, m), 3.03 (2H, m), 8.10 (1H, br), 8.39 (1H, s), 8.42 (1H, s).

25 Reference Example 85

N-[7-[(Dimethylamino)methylidene]-8-oxo-5,6,7,8-tetrahydro-3-quinolinyl]acetamide



The titled compound was obtained by carrying out the
30 same operation as in Reference Example 47, using N-(8-oxo-5,6,7,8-tetrahydro-3-quinolinyl)acetamide obtained in Reference Example 84.

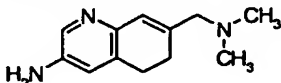
^1H NMR (CDCl_3) δ : 2.09 (3H, s), 2.78 (2H, m), 2.85 (2H, m), 3.10 (6H, s), 7.55 (1H, s), 8.01 (1H, s), 8.56 (1H, s).

147

1m.

Reference Example 86

N-[(3-Amino-5,6-dihydro-7-quinolinyl)methyl]-N,N-dimethylamine

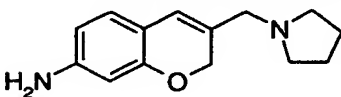


The titled compound was obtained by carrying out the same operation as in Reference Example 41-2), using N-[7-[(dimethylamino)methylidene]-8-oxo-5,6,7,8-tetrahydro-3-quinolinyl]acetamide obtained in Reference Example 85.

^1H NMR (CDCl_3) δ : 2.23 (6H, s), 2.33 (2H, t, $J=8.1$ Hz), 2.78 (2H, t, $J=8.1$ Hz), 2.99 (2H, s), 3.59 (2H, br), 6.43 (1H, s), 6.74 (1H, d, $J=2.5$ Hz), 7.84 (1H, d, $J=2.5$ Hz).

Reference Example 87

3-(1-Pyrrolidinylmethyl)-2H-chromen-7-amine

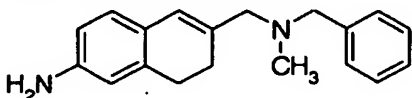


The titled compound was obtained as an oily substance by carrying out the same operations as in Example 41-1), Reference Example 52 and Example 41-2) in this order, using 7-acetylamino-3,4-dihydrochromen-4-one.

^1H -NMR (CDCl_3) δ : 1.77-1.79 (4H, m), 2.45-2.47 (4H, m), 3.11 (2H, s), 3.66 (2H, s), 4.74 (2H, s), 6.14-6.21 (3H, m), 6.75 (1H, d, $J = 7.8$ Hz).

Reference Example 88

6-[(N-Benzyl-N-methylamino)methyl]-7,8-dihydro-2-naphthalenamine



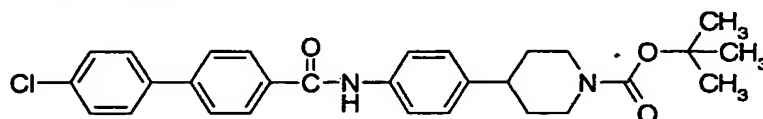
The titled compound was obtained as an oily substance by carrying out the same operation as in Reference Example 52, using 6-acetamido-2-(N,N-dimethylaminomethylidene)-

1-tetralone obtained in Example 41-1).

¹H-NMR (CDCl₃) δ: 2.17 (3H, s), 2.35 (2H, t, J = 8.1 Hz),
2.73 (2H, t, J = 8.1 Hz), 3.04 (2H, s), 3.48 (2H, s), 3.58
(2H, s), 6.29 (1H, s), 6.44 - 6.46 (2H, m), 6.82 (1H, d, J
= 8.1 Hz), 7.03-7.45 (5H, m).

Reference Example 89

4'-Chloro-N-[4-(4-piperidiny)phenyl][1,1'-biphenyl]-
4-carboxamide



10

An ethanol solution (30 ml) of tert-butyl 4-(4-nitrophenyl)-1-piperidinecarboxylate (1.7 g) was subjected to catalytic hydrogenation using 10% palladium carbon (0.2 g) as a catalyst under normal temperature and normal pressure. After the catalyst was filtered off, the filtrate was concentrated to give tert-butyl 4-(4-aminophenyl)-1-piperidinecarboxylate as a viscous oily substance. The titled compound (2.2 g) was obtained as colorless crystals, by carrying out the same operation as in Example 1, using the resulting oily substance and 4'-chloro[1,1'-biphenyl]-4-carboxylic acid (1.43 g).

¹H-NMR (CDCl₃+ DMSO-d₆) δ: 1.05-1.32 (11H, m), 1.38-1.50 (2H, m), 2.20-2.50 (3H, m), 3.75-3.90 (2H, m), 6.81 (2H, d, J=8.4 Hz), 7.07 (2H, d, J=8.4 Hz), 7.20-7.36 (6H, m), 7.69 (2H, d, J=8.1Hz), 9.44 (1H, s).

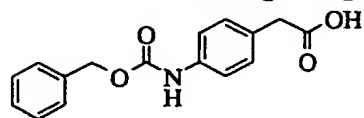
25

Melting point: 232 - 233°C (crystallization solvent : ethyl acetate)

Reference Example 90

2-[4-[[(Benzyloxy)carbonyl]amino]phenyl]ethyl acetate

30

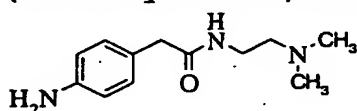


To an ethyl acetate (100 ml) suspension of 4-

aminophenylethyl acetate (10 g), saturated aqueous sodium bicarbonate solution (100 ml) was added, and further, benzyloxycarbonyl chloride (12.3 ml) was added dropwise under ice-cooling. After stirring for 1 hour,
5 hydrochloric acid was added to the reaction mixture to make it acidic, and extraction was conducted using ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was recrystallized from ethyl
10 acetate - hexane, to give the titled compound (17.3 g). Melting point: 148 - 149°C

Reference Example 91

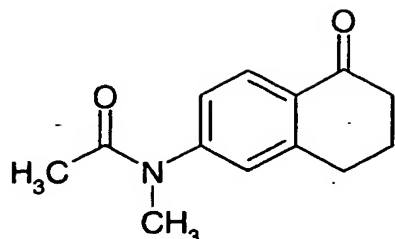
2-(4-Aminophenyl)-N-[2-
15 (dimethylamino)ethyl]acetamide



Pd-C (1 g) was added to a methanol (140 ml) solution of benzyl 4-[2-[[2-(dimethylamino)ethyl]amino]-2-oxoethyl]phenylcarbamate (10 g), which was stirred under
20 hydrogen atmosphere for 1 hour. Pd-C was removed, and the filtrate was concentrated. The residue was purified by alumina column chromatography (development solvent; ethyl acetate:hexane = 1:1), to give the titled compound (6.63 g) as an oily substance.
25 ¹H-NMR(CDCl₃) δ: 2.16 (6H, s), 2.05 (3H, s), 2.30-2.36 (2H, t, J=6.2 Hz), 3.23-3.32 (2H, dd, J=11.4, 6.2 Hz), 3.44 (2H, s), 6.00 (1H, s), 6.63-6.67 (2H, m), 7.00-7.07 (2H, m).

30 Reference Example 92

N-Methyl-N-(5-oxo-5,6,7,8-tetrahydro-2-naphthalenyl)acetamide

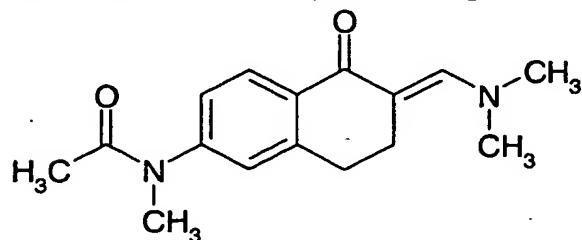


6-Acetamido-1-tetralone (10.0 g, 49.2 mmol) was dissolved in tetrahydrofuran (100 ml). Sodium hydride (oil, 3.0 g) was added to the solution, which was refluxed with heating under nitrogen atmosphere for 2 hours. After cooling, methyl iodide (30 ml) was added to the reaction mixture, which was refluxed with heating under nitrogen atmosphere for 2 hours. The reaction mixture was concentrated. Ethyl acetate and water were added to the residue, and extraction was conducted. The ethyl acetate layer was concentrated, and the residue was purified by alumina column chromatography (development solvent; ethyl acetate:n-hexane = 33:67 ~ 50:50). The product was concentrated under reduced pressure, and the residue was recrystallized from ethyl acetate - diisopropyl ether, to give the titled compound (4.3 g).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.96 (3H, brs), 2.18 (2H, m), 2.69 (2H, t, $J=6.1$ Hz), 2.99 (2H, t, $J=5.9$ Hz), 3.29 (3H, s), 7.01-7.15 (2H, m), 8.08 (1H, d, $J=8.1$ Hz).

Reference Example 93

N-[6-[(Dimethylamino)methylidene]-5-oxo-5,6,7,8-tetrahydro-2-naphthalenyl]-N-methylacetamide



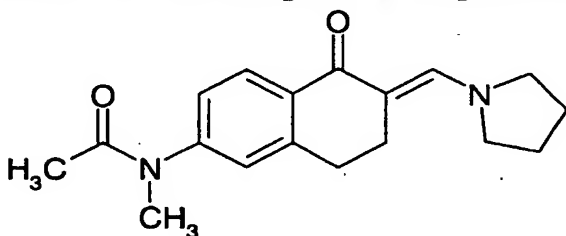
N-Methyl-N-(5-oxo-5,6,7,8-tetrahydro-2-naphthalenyl)acetamide (4.3 g, 19.8 mmol) obtained in Reference Example 92 was dissolved in N,N-

dimethylformamide dimethylacetal (50 ml), which was refluxed with heating under nitrogen atmosphere for 15 hours. The reaction mixture was concentrated, and the residue was washed with ethyl acetate and diisopropyl ether, to give the titled compound (3.9 g).

¹H-NMR (CDCl₃) δ: 1.93 (3H, brs), 2.84 (2H, dd, J=7.5, 5.6 Hz), 2.95 (2H, dd, J=7.5, 5.6 Hz), 3.16 (6H, s), 3.28 (3H, s), 6.99 (1H, s), 7.10 (1H, dd, J=8.1, 2.0 Hz), 7.75 (1H, s), 8.07 (1H, d, J=8.1 Hz).

Reference Example 94

N-Methyl-N-[5-oxo-6-[1-pyrrolidinylmethylidene]-5,6,7,8-tetrahydro-2-naphthalenyl]acetamide



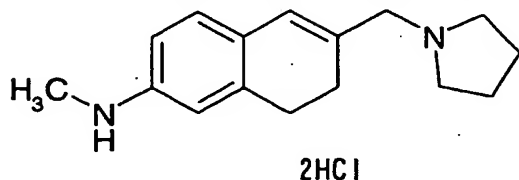
N-[6-[(Dimethylamino)methylidene]-5-oxo-5,6,7,8-tetrahydro-2-naphthalenyl]-N-methylacetamide (5.7 g, 20.9 mmol) obtained in Reference Example 93 was dissolved in pyrrolidine (50 ml), which was refluxed with heating under nitrogen atmosphere for 3.5 hours. Then, ethyl acetate and water were added to the reaction mixture, and extraction was conducted. The ethyl acetate layer was concentrated, and the residue was recrystallized from ethyl acetate - diisopropyl ether, to give the titled compound (4.0 g, yield : 64%).

¹H-NMR (CDCl₃) δ: 1.94 (7H, m), 2.84 (2H, dd, J=7.0, 5.6 Hz), 2.97 (2H, dd, J=7.0, 5.6 Hz), 3.28 (3H, s), 3.63 (4H, m), 6.98 (1H, s), 7.10 (1H, dd, J=8.1, 2.0 Hz), 7.95 (1H, s), 8.08 (1H, d, J=8.1 Hz).

Reference Example 95

N-Methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-

nephthalenamine dihydrochloride

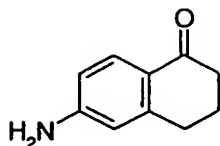


N-Methyl-N-[5-oxo-6-[1-pyrrolidinylmethylidene]-5,6,7,8-tetrahydro-2-naphthalenyl]acetamide (4.0 g, 13.4 mmol) obtained in Reference Example 94 was dissolved in methanol - ethyl acetate (10:1, 220 ml). 10% Palladium carbon (50% wet, 0.4 g) was added to the solution, which was ice cooled. Stirring was began under hydrogen atmosphere, and stirring was conducted for 2 days while returning the temperature of the reaction mixture to room temperature. A catalyst was filtered off, the reaction mixture was concentrated under reduced pressure, and the residue was dissolved in ethyl acetate. Extraction was conducted using 1N hydrochloric acid. The extract was made alkaline with 4N sodium hydroxide solution, and extraction was conducted using ethyl acetate. The extract was concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (100 ml) and 5N hydrochloric acid (100 ml), which was refluxed with heating for 13 hours. The reaction mixture was concentrated. Ethyl acetate and saturated aqueous sodium carbonate solution were added to the residue, and extraction was conducted. The ethyl acetate layer was concentrated. 4N Hydrogen chloride - ethyl acetate solution was added to the resulting oily substance, which was concentrated. The residue was recrystallized from methanol - ethyl acetate, to give the titled compound (2.8 g, yield : 66%).

¹H-NMR (DMSO-d₆) δ: 1.98 (4H, m), 2.45 (4H, m), 2.81 (5H, m), 3.01 (2H, brd), 3.44 (2H, brd), 3.86 (2H, d, J=5.0 Hz), 7.02-7.10 (3H, m), 10.89 (1H, brs).

Reference Example 96

6-Amino-3,4-dihydro-1-(2H)-naphthalenone

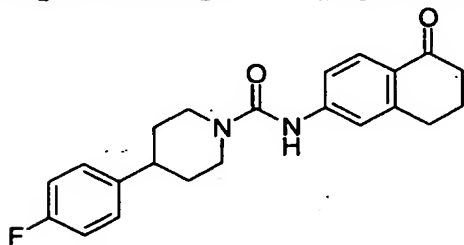


Concentrated hydrochloric acid (250 ml) was added to 6-acetamido-1-tetralone (20.0 g, 98.4 mmol), which was stirred at 100°C for 1 hour. The solvent was distilled out under reduced pressure. Ethyl acetate was added to the residue, which was washed with aqueous potassium carbonate solution and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The residue was powdered with ethyl acetate and isopropyl ether, to give the titled compound (14.5 g).

¹H NMR (CDCl₃) δ: 2.07 (2H, m), 2.57 (2H, m), 2.83 (2H, m), 4.10 (2H, br), 6.42 (1H, d, J=2.2 Hz), 6.53 (1H, dd, J=2.2, 8.4Hz), 7.89 (1H, d, J=8.4 Hz).

Reference Example 97

4-(4-Fluorophenyl)-N-(5-oxo-5,6,7,8-tetrahydro-2-naphthalenyl)-1-piperidinecarboxamide

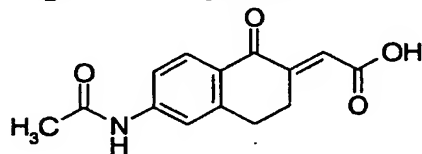


Pyridine(9.95 ml, 123 mmol) and 4-nitrophenyl chloroformate (12.4 g, 61.5 mmol) was added to a tetrahydrofuran(300 ml)solution of 6-amino-3,4-dihydro-1(2H)-naphthalenone(9.92 g, 61.5 mmol)obtained in Reference Example 96, which was stirred at room temperature for 3 hours. The solvent was distilled out under reduced pressure. 1N Hydrochloric acid was added to the residue to powder, which was washed with ethanol. 4N Aqueous sodium hydroxide solution was added to a dimethylsulfoxide (33 ml)solution of the resulting 4-nitrophenyl-5-oxo-

5,6,7,8-tetrahydro-2-naphthalenylcarbamate (2.20 g, 6.74 mmol) and 4-(4-fluorophenyl)piperidine hydrochloride (1.60 g, 7.42 mmol), which was stirred at room temperature for 1 hour. Ethyl acetate was added to the reaction mixture, which was washed with 1N hydrochloric acid, aqueous potassium hydrogencarbonate solution and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and the solvent was distilled out under reduced pressure. The resulting residue was purified by alumina B column chromatography (development solvent; ethyl acetate), and powdered with isopropyl ether and hexane, to give the titled compound (1.89 g).
¹H NMR (CDCl₃) δ: 1.72 (2H, m), 1.92 (2H, m), 2.11 (2H, m), 2.61 (2H, m), 2.72 (1H, m), 2.93 (2H, m), 3.01 (2H, m), 4.23 (2H, m), 6.67 (1H, s), 7.00 (2H, m), 7.12 (3H, m), 7.61 (1H, s), 7.97 (1H, d, J=8.4 Hz).

Reference Example 98

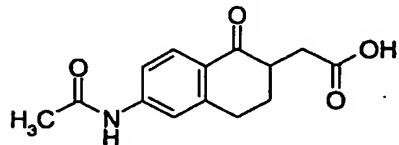
[6-(Acetylamino)-1-oxo-3,4-dihydro-2(1H)-naphthalenylidene]acetic acid



0.5N Aqueous sodium hydroxide solution (190 ml) was added to an aqueous solution (60 ml) of 6-acetamido-1-tetralone (5.00 g, 24.6 mmol) and glyoxylic acid (9.05 g, 98.5 mmol) under ice-cooling, which was stirred at 60°C for 16 hours. After cooling, concentrated hydrochloric acid was added to the reaction mixture. The precipitated crystals were collected, which was washed with water, to give the titled compound (3.73 g).
¹H NMR (DMSO-d₆) δ: 2.10 (3H, s), 2.95 (2H, m), 3.28 (2H, m), 6.63 (1H, s), 7.53 (1H, d, J=8.7Hz), 7.67 (1H, s), 7.91 (1H, d, J=8.7Hz), 10.32 (1H, s), 12.89 (1H, br).

Reference Example 99

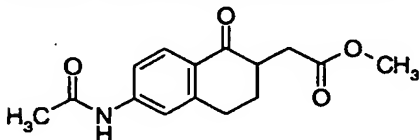
[6-(Acetylamino)-1-oxo-1,2,3,4-tetrahydro-2-naphthalenyl]acetic acid



- 5 70% Acetic acid - water solution (35 ml) of [6-(acetylamino)-1-oxo-3,4-dihydro-2(1H)-naphthalenyliden]acetic acid (3.50 g, 13.5 mmol) obtained in Reference Example 98 and zinc powder (2.1 g) was stirred at 100°C for 30 minutes. After cooling, zinc powder was
10 filtered. Ethyl acetate was added to the filtrate, which was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The resulting oily substance was purified by silica gel column
15 chromatography (development solvent; ethyl acetate : methanol = 10:1), and powdered with ethyl acetate and isopropyl ether, to give the titled compound (2.51 g).
¹H NMR (CDCl₃) δ: 1.85-2.15 (2H, m), 2.08 (3H, s), 2.38 (1H, m), 2.71 (1H, m), 2.88 (2H, m), 3.05 (1H, m), 7.46 (1H, d, J=8.7Hz), 7.60 (1H, s), 7.80 (1H, d, J=8.7Hz), 10.21 (1H, s), 12.09 (1H, br).

Reference Example 100

- 25 Methyl [6-(acetylamino)-1-oxo-1,2,3,4-tetrahydro-2-naphthalenyl]acetate



- Methyl iodide (0.18 ml, 2.87 mmol) was added to a dimethylformamide solution (10 ml) of [6-(acetylamino)-1-oxo-1,2,3,4-tetrahydro-2-naphthalenyl]acetic acid (500
30 mg, 1.91 mmol) obtained in Reference Example 99 and potassium carbonate (529 mg, 3.82 mmol), which was stirred

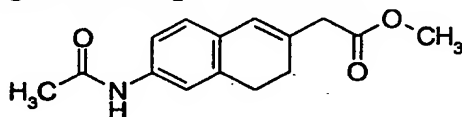
at room temperature for 16 hours. Ethyl acetate was added to the reaction mixture, which was washed with aqueous sodium thiosulfate solution and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure.

The resulting oily substance was purified by alumina B column chromatography (development solvent; ethyl acetate), to give the titled compound (527 mg).

^1H NMR (CDCl_3) δ : 1.98 (1H, m), 2.20 (3H, s), 2.23 (1H, m), 2.47 (1H, m), 3.30 (4H, m), 3.73 (3H, s), 7.21 (1H, d, $J=8.7\text{Hz}$), 7.50-7.80 (2H, m), 7.97 (1H, d, $J=8.7\text{Hz}$).

Reference Example 101

Methyl [6-(acetylamino)-3,4-dihydro-2-naphthalenyl]acetate



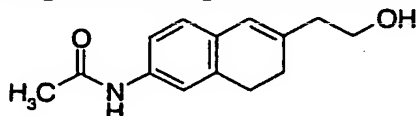
Sodium borohydride (72.4 mg, 1.91 mmol) was added to a methanol solution (10ml) of methyl [6-(acetylamino)-1-oxo-1,2,3,4-tetrahydro-2-naphthalenyl]acetate (527 mg, 1.91 mmol) obtained in Reference Example 100 under ice-cooling, which was stirred for 1 hour. Ethyl acetate was added to the reaction mixture, which was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The resulting oily substance was purified by alumina B column chromatography (development solvent; ethyl acetate). Concentrated sulfuric acid (0.14 ml) was added to an acetic acid solution (7 ml) of the oil (404 mg, 1.46 mmol), which was stirred at 40°C for 5 hours. The solvent was distilled out under reduced pressure. Ethyl acetate was added to the residue, which was washed with aqueous potassium carbonate solution and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was

distilled out under reduced pressure. The resulting oily substance was purified by silica gel column chromatography (development solvent; hexane:ethyl acetate = 1:1), to give the titled compound (251 mg).

5 ¹H NMR (CDCl₃) δ: 2.16 (3H, s), 2.32 (2H, t, J=8.1Hz), 2.82 (2H, t, J=8.1Hz), 3.21 (2H, s), 3.71 (3H, s), 6.30 (1H, s), 6.93 (1H, d, J=8.1Hz), 7.19 (2H, m), 7.33 (1H, s).

Reference Example 102

10 N-[6-(2-Hydroxyethyl)-7,8-dihydro-2-naphthalenyl]acetamide

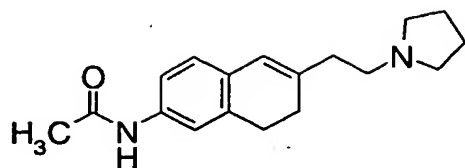


Lithium aluminum hydride (242 mg, 6.38 mmol) was added to a tetrahydrofuran solution (16 ml) of methyl [6-(acetylamino)-3,4-dihydro-2-naphthalenyl]acetate (827 mg, 3.19 mmol) obtained in Reference Example 101 under ice-cooling, which was stirred at room temperature for 1 hour. Ethyl acetate was added to the reaction mixture, which was washed with 1N hydrochloric acid and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The residue was powdered with isopropyl ether, to give the titled compound (364 mg).

15 ¹H NMR (CDCl₃) δ: 1.43 (1H, m), 2.16 (3H, s), 2.26 (2H, t, J=8.1Hz), 2.46 (2H, t, J=6.3Hz), 2.81 (2H, t, J=8.1Hz), 3.78 (2H, m), 6.28 (1H, s), 6.94 (1H, d, J=8.1Hz), 7.08 (1H, br), 7.17 (1H, d, J=8.1Hz), 7.35 (1H, s).

Reference Example 103

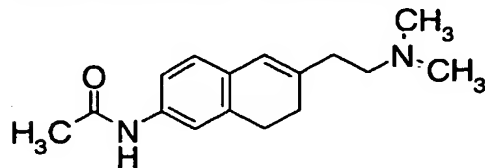
30 N-[6-[2-(1-Pyrrolidinyl)ethyl]-7,8-dihydro-2-naphthalenyl]acetamide



Methanesulfonyl chloride (0.131 ml, 1.69 mmol) was added to a dimethylformamide solution (7 ml) of N-[6-(2-hydroxyethyl)-7,8-dihydro-2-naphthalenyl]acetamide (355 mg, 1.53 mmol) obtained in Reference Example 102 and triethylamine (0.235 ml, 1.69 mmol) under ice-cooling, which was stirred for 30 minutes. Pyrrolidine (0.384 ml, 4.60 mmol) was added to the reaction mixture, which was stirred at 60 °C for 4 hours. The solvent was distilled out under reduced pressure. Ethyl acetate was added to the residue, and extraction was conducted using 1N hydrochloric acid. Potassium carbonate was added to the extract to make it alkaline, and extraction was conducted using ethyl acetate. The extract was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and the solvent was distilled out under reduced pressure. The resulting residue was purified by alumina column chromatography (development solvent; ethyl acetate), to give the titled compound (294 mg).

¹H NMR (CDCl₃) δ: 1.79 (4H, m), 2.16 (3H, s), 2.25 (2H, m), 2.41 (2H, m), 2.55 (4H, m), 2.62 (2H, m), 2.78 (2H, m), 6.20 (1H, s), 6.91 (1H, d, J=8.1Hz), 7.18 (1H, d, J=7.8Hz), 7.32 (2H, m).

Reference Example 104
N-[6-[2-(Dimethylamino)ethyl]-7,8-dihydro-2-naphthalenyl]acetamide



Methanesulfonyl chloride (0.0393 ml, 0.469 mmol) was added to a dimethylformamide solution (2 ml) of N-[6-

(2-hydroxyethyl)-7,8-dihydro-2-naphthalenyl]acetamide (102 mg, 0.426 mmol) obtained in Reference Example 102 and triethylamine (0.0652 ml, 0.469 mmol) under ice-cooling, which was stirred for 30 minutes. A tetrahydrofuran solution (0.64 ml) of 2N dimethylamine was added to the reaction mixture, which was stirred at 60°C for 5 hours.

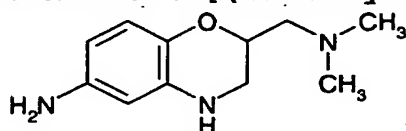
The solvent was distilled out under reduced pressure.

Ethyl acetate was added to the residue, and extraction was conducted using 1N hydrochloric acid. Potassium carbonate was added to the extract to make it alkaline, and extraction was conducted using ethyl acetate. The extract was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and the solvent was distilled out under reduced pressure. The resulting residue was purified by alumina column chromatography (development solvent; ethyl acetate), to give the titled compound (57.5 mg).

¹H NMR (CDCl₃) δ: 2.15 (3H, s), 2.24 (2H, m), 2.29 (6H, s), 2.36 (2H, m), 2.48 (2H, m), 2.78 (2H, m), 6.20 (1H, s), 6.90 (1H, d, J=8.1Hz), 7.20 (1H, d, J=8.1Hz), 7.35 (1H, s), 7.76 (1H, br).

Reference Example 105

6-Amino-2-[(dimethylamino)methyl]-1,4-benzoxazine



1) 2-Ethoxycarbonyl-6-nitro-1,4-benzoxazine (7.20 g, 0.029 mol) obtained by a known method by documents (Journal of heterocyclic chemistry, 19(5), p.1189 (1982)) was dissolved in methanol (50 ml). Sodium borohydride (1.08 g, 0.029 mol) was added to the solution, which was stirred for 2 hours. The reaction mixture was concentrated. Ethyl acetate and aqueous potassium hydrogencarbonate solution were added to the residue, and extraction was conducted. The organic layer was washed

with water, and concentrated. A mixed solution of ethyl acetate and n-hexane (1:5) was added to the residue for crystallization. The crystallized product was collected by filtration, to give 2-hydroxymethyl-6-nitro-1,4-

5 benzoxazine (3.10 g) as a red powder.

¹H-NMR (CDCl₃) δ: 1.96 (1H, m), 3.34-3.49 (2H, m), 3.80-3.90 (2H, m), 4.09 (1H, brs), 4.30-4.40 (1H, m), 6.86 (1H, d, J=8.6 Hz), 7.50 (1H, d, J=2.8 Hz), 7.59 (1H, dd, J=2.8, 8.6 Hz).

10 2) 2-Hydroxymethyl-6-nitro-1,4-benzoxazine (1.00 g, 4.76 mmol) obtained in 1) and triethylamine (708 mg, 7.00 mmol) was dissolved in DMF (30 ml). Methanesulfonyl chloride (545 mg, 4.76 mmol) was added to the solution, which was stirred for 30 minutes. 50% Aqueous
15 dimethylamine solution (3 ml) was added to the reaction mixture, which was stirred at 70°C for 4 hours. Ethyl acetate and water were added to the mixture, and extraction was conducted. The organic layer was washed, and concentrated. The residue was subjected to alumina column chromatography, and eluted with ethyl acetate: n-hexane
20 (40:60), to give 2-[(dimethylamino)methyl]-6-nitro-1,4-benzoxazine (790 mg) as a colorless oily substance.

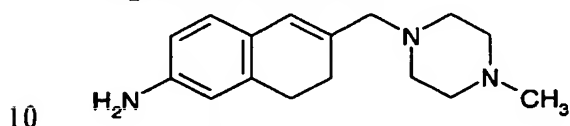
¹H-NMR (CDCl₃) δ: 2.33 (6H, s), 2.47-2.67 (2H, m), 3.19-3.25 (1H, m), 3.46-3.52 (1H, m), 4.09 (1H, brs), 4.30-4.35 (1H, m), 6.86 (1H, d, J=8.9 Hz), 7.48 (1H, d, J=2.8 Hz), 7.57 (1H, dd, J=2.8, 8.9 Hz).

3) 2-[(Dimethylamino)methyl]-6-nitro-1,4-benzoxazine (760 mg, 3.2 mmol) obtained in 2) was dissolved in methanol (10 ml). Concentrated hydrochloric acid (3 ml)
30 and iron powder (0.80 g) were added to the solution, which was stirred for 2 hours. The reaction mixture was concentrated. 1N Aqueous sodium hydroxide solution and ethyl acetate was added to the residue, and extraction was conducted. The organic layer was concentrated. The
35 residue was subjected to alumina column chromatography, and eluted with ethyl acetate: n-hexane (20:80), to give the

titled compound (430 mg) as a colorless oily substance.
¹H-NMR (CDCl₃) δ: 2.31 (6H, s), 2.41-2.62 (2H, m), 3.12-3.17
 (1H, m), 3.36-3.41 (1H, m), 3.30-3.50 (2H, brs), 3.67 (1H,
 brs), 4.12-4.21 (1H, m), 5.99 (1H, d, J=2.5 Hz), 6.03 (1H,
 5 dd, J=2.5, 8.4 Hz), 6.65 (1H, d, J=8.4 Hz).

Reference Example 106

6-[(4-Methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenamine

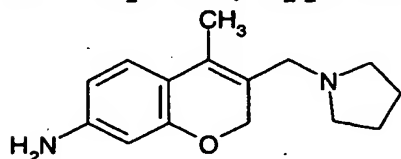


The titled compound was obtained by carrying out the same operation as in Reference Example 52, using 6-acetamido-2-(N,N-dimethylaminomethylidene)-1-tetralone obtained in Example 41-1).

15 ¹H NMR (CDCl₃) δ: 2.27 (2H, t, J=8.1 Hz), 2.29 (3H, s), 2.45 (8H, bs), 2.72 (2H, t, J=8.1 Hz), 3.03 (2H, s), 3.60 (2H, s), 6.26 (1H, s), 6.45-6.47 (2H, m), 6.80-6.83 (1H, m).

Reference Example 107

20 4-Methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-amine



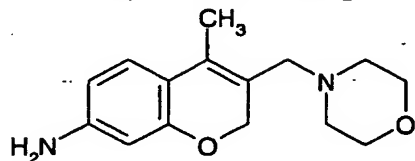
The titled compound was obtained by carrying out the same operations as in Example 41-1) and Reference Example 69 in this order, using 1-acetylamino-3,4-dihydrochromen-1-one.

25 ¹H NMR (CDCl₃) δ: 1.73-1.83 (4H, m), 1.99 (3H, s), 2.46-2.51 (4H, m), 3.22 (2H, s), 3.70 (2H, bs), 4.66 (2H, s), 6.18 (1H, d, J=2.2 Hz), 6.26 (1H, dd, J=2.2 Hz, 8.1 Hz), 7.00 (1H, d, J=8.1 Hz).

30

Reference Example 108

4-Methyl-3-(4-morpholinylethyl)-2H-chromen-7-amine

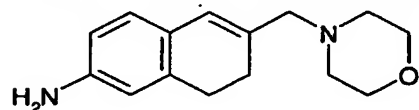


The titled compound was obtained by carrying out the same operations as in Example 41-1) and Reference Example 69 in this order, using 1-acetylamino-3,4-dihydrochromen-1-one.

^1H NMR (CDCl_3) δ : 1.98 (3H, s), 2.41-2.44 (4H, m), 3.08 (2H, s), 3.66-3.69 (6H, m), 4.62 (2H, s), 6.18 (1H, d, $J=2.2$ Hz), 6.26 (1H, dd, $J=2.2$ Hz, 8.1 Hz), 7.00 (1H, d, $J=8.1$ Hz).

Reference Example 109

6-(4-Morpholinylmethyl)-7,8-dihydro-2-naphthalenamine

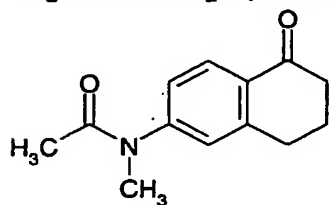


The titled compound was obtained by carrying out the same operations as in Reference Example 52, using 6-acetamido-2-(N,N -dimethylaminomethylidene)-1-tetralone obtained in Example 41-1).

^1H -NMR (CDCl_3) δ : 2.28 (2H, t, $J=7.8$ Hz), 2.42 (4H, t, $J=4.4$ Hz), 2.72 (2H, t, $J=7.8$ Hz), 3.01 (2H, s), 3.60 (2H, brs.), 3.70 (4H, t, $J=4.4$ Hz), 6.26 (1H, s), 6.46 (2H, m), 6.82 (1H, d, $J=8.7$ Hz).

Reference Example 110

N-Methyl-N-(5-oxo-5,6,7,8-tetrahydro-2-naphthalenyl)acetamide



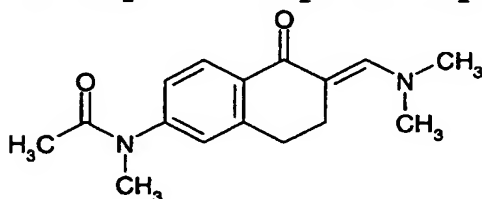
6-Acetamido-1-tetralone (13.7 g, 67.4 mmol) was dissolved in tetrahydrofuran (40 ml). Sodium

hydride(oil)(2.40 g, 101 mmol) was added to the solution, which was refluxed with heating for 2.5 hours. After cooling, methyl iodide(20 ml)was added to the reaction mixture, which was stirred at 40°C for 15 hours. The
5 reaction mixture was poured into a cold water, and extraction was conducted using ethyl acetate. The extract was washed with 1N hydrochloric acid and 1 N aqueous sodium hydroxide solution. The ethyl acetate layer was concentrated. The residue was purified by alumina column
10 chromatography (development solvent; ethyl acetate:n-hexane = 50:50 ~ 100:0) . The eluent was concentrated under reduced pressure. The resulting residue was recrystallized from ethyl acetate - diisopropyl ether, to give the titled compound(8.3 g).

15 ¹H-NMR (CDCl₃) δ : 1.96 (3H, s), 2.19(2H, m), 2.69 (2H, t, J=6.2 Hz), 2.99 (2H, t, J=5.9 Hz), 3.29 (3H, s), 7.10-7.15 (2H, m), 8.09 (1H, d, J=8.4 Hz).

Reference Example 111

20 N-[6-[(E)-(Dimethylamino)methylidene]-5-oxo-5,6,7,8-tetrahydro-2-naphthalenyl]-N-methylacetamide



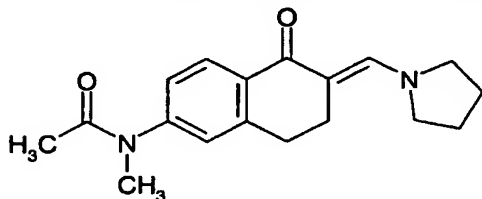
N-Methyl-N-(5-oxo-5,6,7,8-tetrahydro-2-naphthalenyl)acetamide (4.3 g, 19.8 mmol) obtained in
25 Reference Example 110 was dissolved in N,N-dimethylformamide-dimethylacetal(50 ml), which was refluxed with heating under nitrogen atmosphere for 15 hours. The reaction mixture was concentrated under reduced pressure. The resulting residue was washed with
30 ethyl acetate - diisopropyl ether, to give the titled compound(3.9 g).

¹H-NMR (CDCl₃) δ : 1.93 (3H, s), 2.86 (2H, t, J=7.3 Hz), 2.95

(2H, t, $J=7.3$ Hz), 3.16 (6H, s), 3.28 (3H, s), 6.99 (1H, s), 7.09 (1H, d, $J=8.1$ Hz), 7.75 (1H, s), 8.07 (1H, d, $J=8.1$ Hz).

5 Reference Example 112

N-Methyl-N-[5-oxo-6-((E)-1-pyrrolidinylmethylidene)-5,6,7,8-tetrahydro-2-naphthalenyl]acetamide

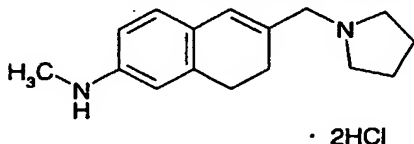


10 N-[6-[(E)-(Dimethylamino)methylidene]-5-oxo-5,6,7,8-tetrahydro-2-naphthalenyl]-N-methylacetamide (5.7 g, 20.9 mmol) obtained in Reference Example 111 was dissolved in pyrrolidine (50 ml), which was refluxed with heating under nitrogen atmosphere for 3.5 hours. The reaction mixture was poured into cold water, and extraction was conducted using ethyl acetate. The ethyl acetate layer was concentrated. The resulting residue was recrystallized from ethyl acetate - diisopropyl ether, to give the titled compound (4.0 g).

15 $^1\text{H-NMR}$ (CDCl_3) δ : 1.93-1.96 (7H, m), 2.85 (2H, t, $J=6.7$ Hz), 2.96 (2H, t, $J=6.7$ Hz), 3.28 (3H, s), 3.63 (4H, m), 6.99 (1H, s), 7.10 (1H, dd, $J=8.4, 2.0$ Hz), 7.95 (1H, s), 8.08 (1H, d, $J=8.4$ Hz).

Reference Example 113

25 N-Methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine dihydrochloride

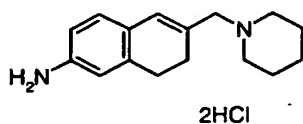


30 N-Methyl-N-[5-oxo-6-((E)-1-pyrrolidinylmethylidene)-5,6,7,8-tetrahydro-2-naphthalenyl]acetamide (4.0 g, 13.4 mmol) obtained in

Reference Example 112 was dissolved in methanol - acetic acid(10:1, 220 ml). 10% Palladium on carbon (0.4 g) was added to the solution, which was stirred under hydrogen atmosphere for 48 hours. The catalyst was filtered off, and
5 the reaction mixture was concentrated under reduced pressure. Ethyl acetate and 1N hydrochloric acid were added to the residue, and extraction was conducted. After the water layer was made alkaline with 4N aqueous sodium hydroxide solution, extraction was conducted using ethyl
10 acetate. The ethyl acetate layer was concentrated. Tetrahydrofuran - 5N hydrochloric acid (50:50, 200 ml) was added to the resulting residue, which was refluxed with heating for 13 hours. The reaction mixture was concentrated. Ethyl acetate and saturated aqueous sodium
15 carbonate solution was added to the residue, and extraction was conducted. 4N Hydrogen chloride - ethyl acetate solution was added to the ethyl acetate layer, which was concentrated under reduced pressure. The resulting residue was recrystallize(from methanol - ethyl acetate,
20 to give the titled compound(2.8 g).
¹H-NMR (DMSO-d₆) δ: 1.98 (4H, m), 2.45 (4H, m), 2.81 (5H, m), 3.01 (2H, m), 3.44 (2H, m), 3.85 (1H, s), 3.86 (1H, s), 6.67 (1H, s), 7.02-7.10 (3H, m), 10.90 (1H, brs.).

25 Reference Example 114

6-(1-Piperidinylmethyl)-7,8-dihydro-2-naphthalenamine dihydrochloride



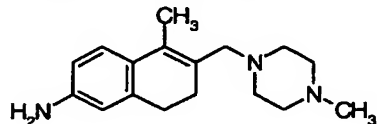
The titled compound was obtained by carrying out the
30 same operation as in Reference Example 52, using 6-acetamido-2-(N,N-dimethylaminomethylidene)-1-tetralone obtained in Example 41-1).

¹H-NMR (DMSO-d₆) δ: 1.39 (1H, m), 1.80 (5H, m), 2.50 (5H, m), 2.83 (4H, m), 3.35-3.38 (2H, m), 3.79 (2H, s), 6.70 (1H,

s), 7.05-7.13 (3H, m), 10.40 (1H, brs).

Reference Example 115

5-Methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenamine

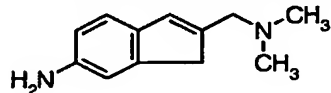


The titled compound was obtained by carrying out the same operation as in Reference Example 69, using 6-acetamido-2-(N,N-dimethylaminomethylidene)-1-tetralone obtained in Example 41-1).

¹H NMR (CDCl₃) δ: 2.02 (3H, s), 2.27 (2H, t, J=8.1 Hz), 2.27 (3H, s), 2.44 (8H, bs), 2.63 (2H, t, J=8.1 Hz), 3.12 (2H, s), 3.61 (2H, s), 6.48-6.54 (2H, m), 7.08 (1H, d, J=7.8 Hz).

Reference Example 116

2-[(Dimethylamino)methyl]-1H-inden-6-amine

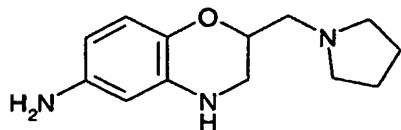


The titled compound was obtained by carrying out the same operation as in Example 41-2), using N-[2-[(E)-(dimethylamino)methylidene]-1-oxo-2,3-dihydro-1H-inden-5-yl]acetamide obtained in Reference Example 47.

¹H NMR (CDCl₃) δ: 2.24 (6H, s), 3.26 (2H, s), 3.33 (2H, s), ca.3.5 (2H, br), 6.58 (2H, m), 6.81 (1H, s), 7.08 (1H, d, J=8.1 Hz).

Reference Example 117

6-Amino-2-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-1,4-benzoxazine



A mixture of 6-nitro-2-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-1,4-benzoxazine and 4-(methylsulfonyl)-

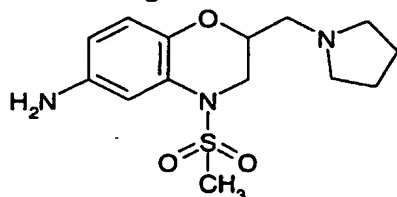
6-nitro-2-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-1,4-benzoxazine was obtained by carrying out the same operation as in Reference Example 105-2), using 2-hydroxymethyl-6-nitro-3,4-dihydro-2H-1,4-benzoxazine obtained in
5 Reference Example 105-1).

The titled compound was obtained by carrying out the same operation as in Reference Example 105-3), using the mixture obtained above.

¹H-NMR (CDCl₃) δ: 1.76-1.81 (4H, m), 2.50-2.70 (4H, m), 2.70
10 (2H, d, J=6.3Hz), 3.13-3.20 (1H, m), 3.20-3.40 (2H, brs), 3.39-3.43 (1H, m), 3.66 (1H, brs), 4.11-4.21 (1H, m), 5.99 (1H, d, J=2.7Hz), 6.03 (1H, dd, J=2.7, 8.4 Hz), 6.64 (1H, d, J=8.4 Hz).

15 Reference Example 118

6-Amino-4-(methylsulfonyl)-2-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-1,4-benzoxazine

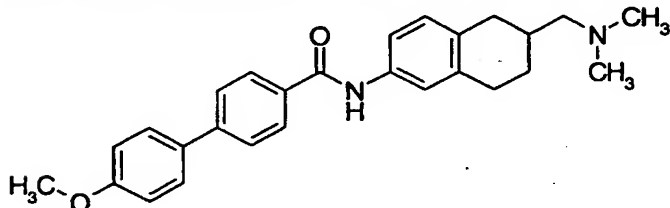


The titled compound was obtained by carrying out the same operation as in Reference Example 105-3), using the
20 mixture of 6-nitro-2-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-1,4-benzoxazine and 4-(methylsulfonyl)-6-nitro-2-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-1,4-benzoxazine obtained in Reference Example 117.

25 ¹H-NMR (CDCl₃) δ: 1.70-1.80 (4H, m), 2.50-2.70 (4H, m), 2.73 (2H, d, J=6.0Hz), 2.95 (3H, s), 3.21-3.29 (1H, m), 2.80-3.10 (2H, brs), 4.10-4.21 (1H, m), 4.26-4.32 (1H, m), 6.43 (1H, dd, J=2.7, 8.4 Hz), 6.77 (1H, d, J=8.4 Hz), 7.11 (1H, d, J=2.7Hz).

Example 1

N-[2-(N,N-Dimethylamino)methyl-6-tetralinyl]-(4'-methoxybiphenyl-4-yl)carboxamide



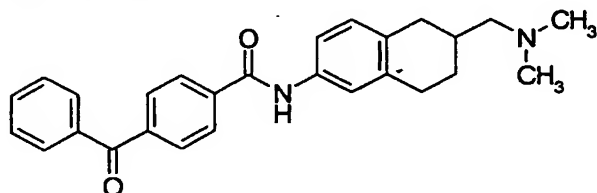
5 DMF solution (0.25 ml) of 2M HOBT, DMF solution (0.30 ml) of 2M WSCD, triethylamine (0.14 ml) and DMAP (0.132 g) were added to DMF solution (3 ml) of 6-amino-2-(N,N-dimethylamino)methyltetralin (0.139 g) and 4-(4-methoxyphenyl)benzoic acid (0.118 g). After the reaction mixture
10 was stirred at room temperature for 12 hours, 10% potassium carbonate solution was added, and extraction was conducted using ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The resulting crude crystal
15 was washed with diethyl ether, which was recrystallized using ethyl acetate-hexane, to give the titled compound (0.124 g).

Melting point: 170 - 175°C.

20 Compounds described in the following Examples 2 and 3 were produced in the same manner as in Example 1.

Example 2

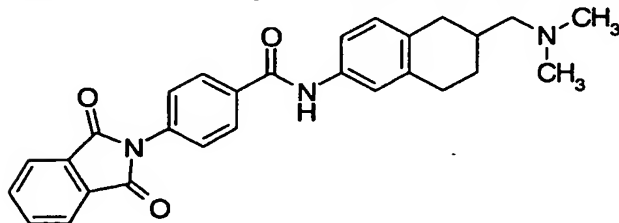
4-Benzoyl-N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]
25 benzamide



Melting point: 193 - 196°C (recrystallization solvent: ethyl acetate-hexane)

Example 3

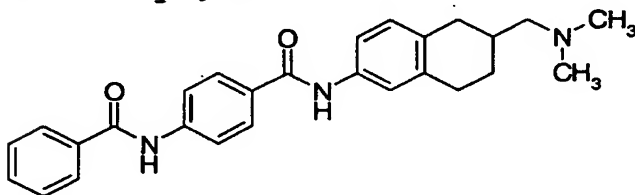
N-[2-(N,N-Dimethylamino)methyl-6-tetralinyl]-4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl) benzamide



5 Melting point: 235 - 240°C (washed with diethyl ether)

Example 4

4-(Benzoylamino)-N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]benzamide



10

6-Amino-2-(N,N-dimethylamino)methyltetralin hydrochloride (139 mg), 4-benzoylamino benzoic acid (121 mg), WSCD (0.13 ml), HOBt (92 mg), triethylamine (0.14 ml) and DMAP (61 mg) were added to DMF (4 ml). After the reaction mixture was shaken at room temperature for 20 hours using a shaker, the reaction mixture was poured into water, and extraction was conducted using ethyl acetate-THF (1:1).

15

The organic layer was washed with water, saturated sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried, and then concentrated. The resulting crude crystal was washed with hexane, to give the titled compound (181 mg).

20

Melting point : 241 - 242°C

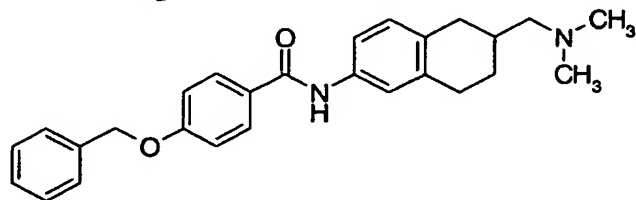
Washing solvent : hexane

25

Compounds described in the following Examples 5 to 14 were produced in the same manner as in Example 4.

Example 5

4-(Benzyloxy)-N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]benzamide

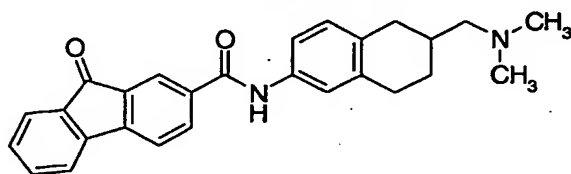


5 Melting point : 135 - 136°C

Washing solvent : hexane

Example 6

10 N-[2-(N,N-Dimethylamino)methyl-6-tetralinyl]-9-oxo-9H-fluoren-2-carboxamide

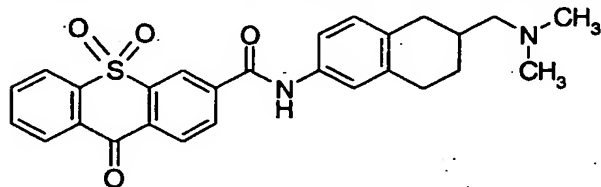


Melting point : 224 - 226°C

Washing solvent : hexane

15 Example 7

N-[2-(N,N-Dimethylamino)methyl-6-tetralinyl]-9,10,10-trioxo-9,10-dihydro-101⁶-thioxanthene-3-carboxamide



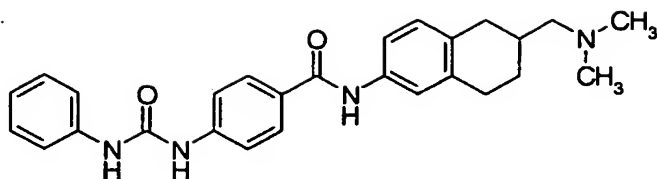
Melting point : 222 - 223°C (decomposition)

20 Washing solvent: hexane

Example 8

(4-Anilinocarbonyl)amino-N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]benzamide

171

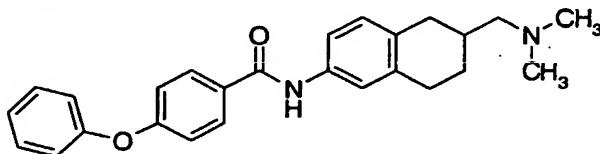


Melting point : 216 - 217°C (decomposition)

Washing solvent : hexane

5 Example 9

N-[2-(N,N-Dimethylamino)methyl-6-tetralinyl]-4-phenoxybenzamide

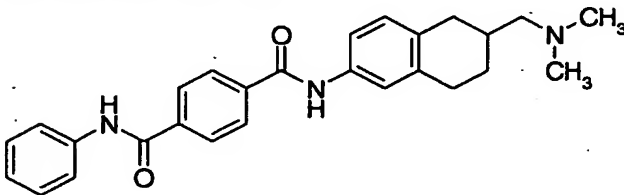


Melting point : 137 - 139°C

10 Washing solvent : hexane

Example 10

N¹-[2-(N,N-Dimethylamino)methyl-6-tetralinyl]-N⁴-phenyl terephthalamide



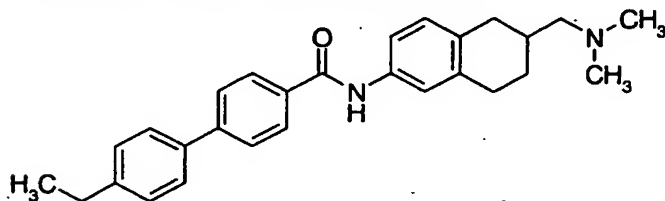
15

Melting point : 238 - 240°C (decomposition)

Washing solvent : hexane

Example 11

20 (4'-Ethylbiphenyl-4-yl)-N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]carboxamide

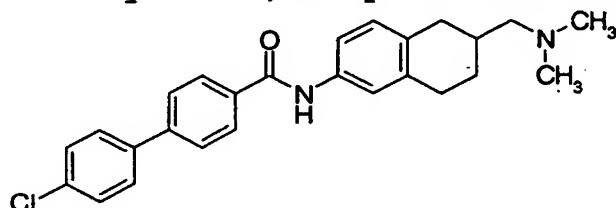


Melting point : 137 - 138°C

Washing solvent : hexane

Example 12

(4'-Chlorobiphenyl-4-yl)-N-[2-(N,N-
5 dimethylamino)methyl-6-tetralinyl]carboxamide

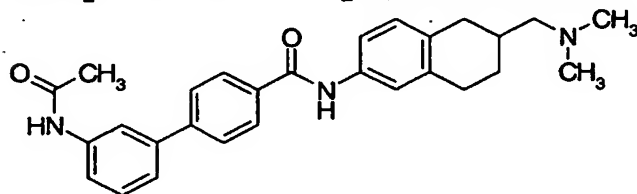


Melting point : 187 - 189°C

Washing solvent : hexane

10 Example 13

(4'-Acetaminobiphenyl-4-yl)-N-[2-(N,N-dimethylamino)
methyl-6-tetralinyl]carboxamide

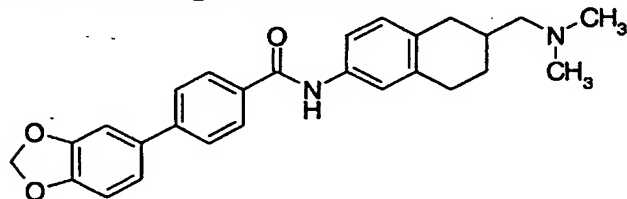


Melting point : 183 - 186°C

15 Washing solvent : hexane

Example 14

4-(1,3-Benzodioxol-5-yl)-N-[2-N,N-dimethylamino)methyl-
6-tetralinyl]benzamide



20

Melting point : 174 - 176°C

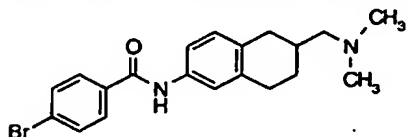
Washing solvent : hexane

Example 15

25 4-Bromo-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-

tetrahydro-2-naphthalenyl]benzamide

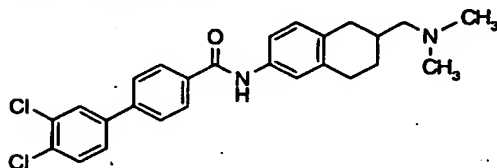
The titled compound was obtained as a white powder by the same method as in Example 1.



5 Melting point: 141 - 143°C (washing solvent: n-hexane)

Example 16

3',4'-Dichloro-N-[6-[(N,N-dimethylamino)methyl]-
5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-
10 carboxamide



4-Bromo-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-
tetrahydro-2-naphthalenyl]benzamide (400 mg, 1.03 mmol)
obtained in Example 15, 3,4-dichlorophenylboric acid (50
15 wt% THF-H₂O solution, 0.473 ml, 1.24 mmol), and 2N sodium
carbonate solution (1.03 ml, 2.07 mmol) were dissolved in
50 ml of dimethoxyethane, then palladium
tetrakis(triphenyl)phosphine (35.8 mg, 0.031 mmol) was added
under nitrogen atmosphere, which was stirred at 90°C for
20 15 hours.

Ethyl acetate was added to the reaction mixture, which
was washed with saturated aqueous sodium chloride solution,
dried using anhydrous magnesium sulfate, and the solvent
was distilled out under reduced pressure. The residue was
25 refined by alumina column chromatography (development
solvent; n-hexane:ethyl acetate = 3:1), and pulverized with
n-hexane to give the titled compound (204 mg) a white
powder.

¹H-NMR (CDCl₃) δ: 1.41 (1H, m), 1.95 (2H, m), 2.26 (6H, s),
30 2.26-2.45 (3H, m), 2.83-2.99 (3H, m), 7.10 (1H, d, J=8.1
Hz), 7.26-7.77 (8H, m), 7.94 (2H, d, J=8.4 Hz).

Elemental analysis for $C_{26}H_{26}Cl_2N_2O \cdot 0.1H_2O$

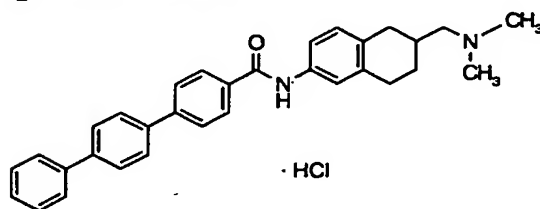
Calcd.: C, 68.60; H, 5.80; N, 6.15.

Found: C, 68.42; H, 5.60; N, 5.92.

Melting point: 143 - 145°C (crystallization solvent:
ethyl acetate-hexane)

Example 17

N-[6-[(N,N-Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4'-phenyl[1,1'-biphenyl]-4-carboxamide
hydrochloride



The free basic substance (35 mg) of the titled compound was obtained in the same manner as in Example 16, using 4-bromo-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]benzamide (400 mg, 1.03 mmol) obtained in Example 15, and 4-biphenylboric acid (1.25 g, 1.25 mmol). The resulting free basic substance (30 mg) was dissolved in 10 ml of methanol, then 100 ml of 1N hydrochloric acid was added, and the reaction mixture was stirred. The reaction mixture was concentrated, and pulverized using diethyl ether, to give the titled compound (35.3 mg) as a white powder.

1H -NMR (DMSO- d_6 , free base) δ : 1.32 (1H, m), 1.93 (2H, m), 2.15 (6H, s), 2.15-2.36 (3H, m), 2.74-2.94 (3H, m), 7.05 (1H, d, $J=8.4$ Hz), 7.40-7.55 (5H, m), 7.73-7.91 (8H, m), 8.07 (2H, d, $J=8.4$ Hz), 10.14 (1H, s).

Elemental analysis for $C_{32}H_{32}N_2O \cdot HCl \cdot 2H_2O$

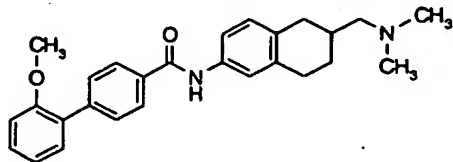
Calcd.: C, 72.10; H, 7.00; N, 5.25.

Found: C, 71.81; H, 6.57; N, 5.08.

Melting point: 220°C (decomposition) (crystallization solvent: methanol-diethyl ether)

Example 18

N-[6-[(N,N-Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-2'-methoxy[1,1'-biphenyl]-4-carboxamide



5 The titled compound (208 mg) was obtained as a white powder by the same method as in Example 16, using 4-bromo-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]benzamide (250 mg, 0.645 mmol) obtained in Example 15, and 2-methoxyphenylboric acid (118
10 mg, 0.775 mmol).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.42 (1H, m), 1.96 (2H, m), 2.23 (6H, s), 2.23-2.47 (3H, m), 2.85 (3H, m), 3.83 (3H, s), 7.05 (3H, m), 7.34 (3H, m), 7.47 (1H, s), 7.64 (2H, d, $J=8.4$ Hz), 7.79 (1H, s), 7.90 (2H, d, $J=8.4$ Hz).

15 Elemental analysis for $\text{C}_{27}\text{H}_{30}\text{N}_2\text{O}_2 \cdot 0.1\text{H}_2\text{O}$

Calcd.: C, 77.89; H, 7.31; N, 6.73.

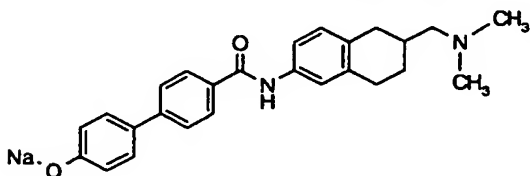
Found: C, 77.86; H, 7.18; N, 6.79.

Melting point: 155 - 157°C (crystallization solvent: ethyl acetate-hexane)

20

Example 19

Sodium salt of N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4'-oxy[1,1'-biphenyl]-4-carboxamide



25

The titled compound (117 mg) was obtained as a white powder by the same method as in Example 16, using 4-bromo-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]benzamide (250 mg, 0.645 mmol)
30 and 4-hydroxyphenylboric acid (107 mg, 0.775 mmol).

¹H-NMR (DMSO-d₆) δ : 1.36 (1H, m), 1.89 (2H, m), 2.15 (6H, s), 2.15-2.35 (3H, m), 2.77 (3H, m), 6.88 (2H, d, J=8.4 Hz), 7.02 (1H, d, J=8.4 Hz), 7.48 (1H, d, J=8.4 Hz), 7.53 (1H, s), 7.59 (2H, d, J=8.4 Hz), 7.73 (2H, d, J=8.4 Hz), 8.00 (2H, d, J=8.4 Hz), 10.07 (1H, s).

Elemental analysis for C₂₆H₂₇N₂O₂Na · 0.2H₂O

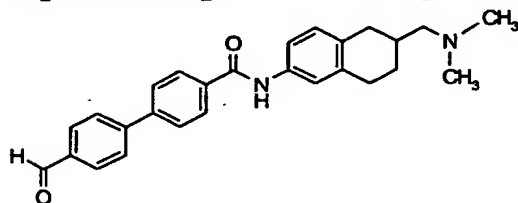
Calcd.: C, 73.29; H, 6.48; N, 6.59.

Found: C, 73.25; H, 6.18; N, 6.36.

Melting point: 246 - 248°C (crystallization solvent: ethyl acetate-diethyl ether)

Example 20

N-[6-[(N,N-Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4'-formyl[1,1'-biphenyl]-4-carboxamide



The titled compound (205 mg) was obtained as a white powder by the same method as in Example 16, using 4-bromo-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]benzamide (250 mg, 0.645 mmol) and 4-formylphenylboric acid (145 mg, 0.968 mmol).

¹H-NMR (CDCl₃) δ : 1.41 (1H, m), 1.95 (2H, m), 2.26 (6H, s), 2.26-2.42 (3H, m), 2.85-2.94 (3H, m), 7.09 (2H, d, J=8.1 Hz), 7.32 (1H, d, J=8.4 Hz), 7.47 (1H, m), 7.63-7.94 (3H, m), 7.87-7.99 (4H, m), 8.13 (1H, s), 10.11 (1H, s).

Elemental analysis for C₂₇H₂₈N₂O₂ · 0.2H₂O

Calcd.: C, 77.93; H, 6.88; N, 6.73.

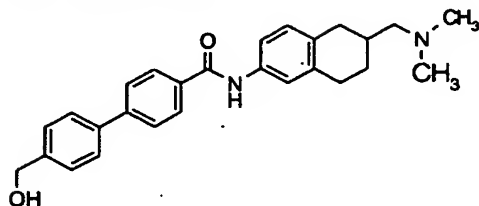
Found: C, 77.89; H, 6.75; N, 6.71.

Melting point: 130 - 132°C (crystallization solvent: ethyl acetate-diethyl ether)

Example 21

N-[6-[(N,N-Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-

naphthalenyl]-4'-(hydroxymethyl)[1,1'-biphenyl]-4-carboxamide



N-[6-[(N,N-Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4'-formyl[1,1'-biphenyl]-4-carboxamide (100 mg, 0.242 mmol) was dissolved in tetrahydrofuran-methanol (1:1) solution (2.4 ml), then sodium borohydride (18.3 mg, 0.485 mmol) was added, which was stirred for 2 hours. Ethyl acetate was added to the reaction mixture, which was washed with saturated aqueous sodium chloride solution, dried using anhydrous magnesium sulfate, and the solvent was distilled out under reduced pressure. The residue was pulverized using ether-n-hexane, to give the titled compound (86 mg) as a white powder.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.39 (1H, m), 1.94 (2H, m), 2.25 (6H, s), 2.25-2.44 (3H, m), 2.82-2.95 (3H, m), 4.78 (2H, s), 7.07 (1H, d, $J=8.4$ Hz), 7.31 (1H, d, $J=8.4$ Hz), 7.38-7.56 (4H, m), 7.64-7.70 (3H, m), 7.85 (1H, s), 7.93 (2H, d, $J=8.4$ Hz).

Elemental analysis for $\text{C}_{27}\text{H}_{30}\text{N}_2\text{O}_2 \cdot 0.2\text{H}_2\text{O}$

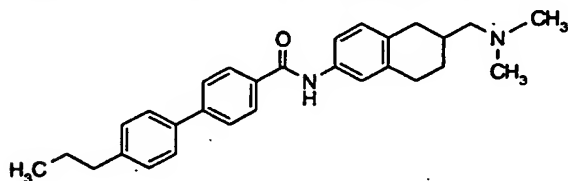
Calcd.: C, 77.56; H, 7.33; N, 6.70.

Found: C, 77.53; H, 7.27; N, 6.55.

Melting point: 138 - 139°C (crystallization solvent: ethyl acetate-diethyl ether)

Example 22

N-[6-[(N,N-Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4'-propyl[1,1'-biphenyl]-4-carboxamide



The titled compound (158 mg) was obtained as a white powder by the same method as in Example 1, using N-[(6-amino-1,2,3,4-tetrahydro-2-naphthalenyl)methyl]-N,N-dimethylamine (102 mg, 0.499 mmol), and 4-(4-propyl)benzoic acid (144 mg, 0.599 mmol).

¹H-NMR (CDCl₃) δ: 0.98 (3H, t, J=7.5 Hz), 1.40 (1H, m), 1.69 (2H, m), 1.94 (2H, m), 2.25 (6H, s), 2.25-2.45 (3H, m), 2.64 (2H, t, J=7.5 Hz), 2.85 (3H, m), 7.08 (1H, d, J=7.8 Hz), 7.26 (3H, m), 7.46 (1H, s), 7.54 (2H, d, J=8.1 Hz), 7.67 (2H, d, J=8.1 Hz), 7.81 (1H, s), 7.91 (2H, d, J=8.4 Hz).

Elemental analysis for C₂₉H₃₄N₂O

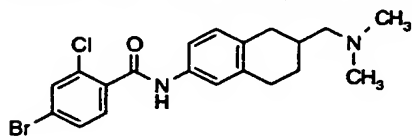
Calcd.: C, 81.65; H, 8.03; N, 6.57.

Found: C, 81.30; H, 7.94; N, 6.40.

Melting point: 186 - 188°C (crystallization solvent: ethyl acetate-diethyl ether)

Example 23

4-Bromo-2-chloro-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]benzamide



The titled compound (483 mg) was obtained as a white powder by the same method as in Example 1, using N-[(6-amino-1,2,3,4-tetrahydro-2-naphthalenyl)methyl]-N,N-dimethylamine (300 mg, 1.47 mmol) and 4-bromo-2-chloro benzoic acid (415 mg, 1.76 mmol).

¹H-NMR (CDCl₃) δ: 1.40 (1H, m), 1.94 (2H, m), 2.25 (6H, s), 2.25-2.44 (3H, m), 2.94 (3H, m), 7.08 (1H, d, J=8.4 Hz), 7.28 (1H, m), 7.41 (1H, s), 7.50 (1H, m), 7.61 (2H, m), 7.81 (1H, s).

Elemental analysis for C₂₀H₂₂BrClN₂O

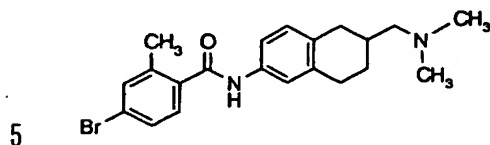
Calcd.: C, 56.96; H, 5.26; N, 6.64.

Found: C, 57.09; H, 5.37; N, 6.55.

Melting point: 130 - 132°C (crystallization solvent: ethyl acetate-diethyl ether)

Example 24

4-Bromo-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-2-methylbenzamide



The titled compound (418 mg) was obtained as a white powder by the same method as in Example 1, using N-[(6-amino-1,2,3,4-tetrahydro-2-naphthalenyl)methyl]-N,N-dimethylamine (293 mg, 1.43 mmol) and 4-bromo-2-methyl benzoic acid (370 mg, 1.72 mmol).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.40 (1H, m), 2.04 (2H, m), 2.25 (6H, s), 2.25-2.40 (3H, m), 2.46 (3H, s), 2.88 (3H, m), 7.07 (1H, d, $J=7.8$ Hz), 7.21-7.41 (6H, m).

Elemental analysis for $\text{C}_{21}\text{H}_{25}\text{BrN}_2\text{O}$

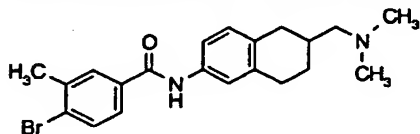
15 Calcd.: C, 62.85; H, 6.28; N, 6.98.

Found: C, 63.10; H, 6.11; N, 6.97.

Melting point: 140 - 142°C (crystallization solvent: ethyl acetate-hexane)

20 Example 25

4-Bromo-N-[6[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-3-methylbenzamide



25 The titled compound (434 mg) was obtained as a white powder by the same method as in Example 1, using N-[(6-amino-1,2,3,4-tetrahydro-2-naphthalenyl)methyl]-N,N-dimethylamine (300 mg, 1.47 mmol) and 4-bromo-3-methyl benzoic acid (379 mg, 1.76 mmol).

30 $^1\text{H-NMR}$ (CDCl_3) δ : 1.40 (1H, m), 1.93 (2H, m), 2.25 (6H, s), 2.25-2.40 (3H, m), 2.46 (3H, s), 2.87 (3H, m), 7.07 (1H, d, $J=7.8$ Hz), 7.29 (1H, m), 7.40 (1H, s), 7.49 (1H, m), 7.61 (1H, d, $J=8.1$ Hz), 7.72 (2H, s-like).

Elemental analysis for $C_{21}H_{25}BrN_2O$

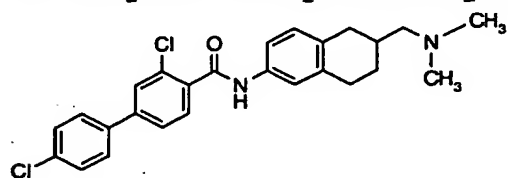
Calcd.: C, 62.85; H, 6.28; N, 6.98.

Found: C, 62.84; H, 6.05; N, 6.93.

Melting point: 154 - 155°C (crystallization solvent: ethyl acetate-hexane)

Example 26

3,4'-Dichloro-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound (122 mg) was obtained as a white powder by the same method as in Example 16, using 4-bromo-2-chloro-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]benzamide (250 mg, 0.607 mmol) obtained in Example 23, and 4-chlorophenyl boric acid (114 mg, 0.725 mmol).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.41 (1H, m), 1.95 (2H, m), 2.26 (6H, s), 2.26-2.42 (3H, m), 2.85 (3H, m), 7.10 (1H, d, $J=8.4$ Hz), 7.31 (1H, m), 7.43-7.63 (8H, m), 7.87 (1H, d, $J=8.1$ Hz).

Elemental analysis for $C_{26}H_{26}Cl_2N_2O$

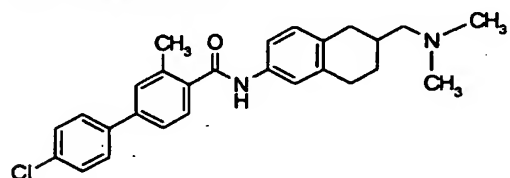
Calcd.: C, 68.87; H, 5.78; N, 6.18.

Found: C, 68.61; H, 5.49; N, 6.10.

Melting point: 177 - 179°C (crystallization solvent: ethyl acetate-diethyl ether)

Example 27

4'-Chloro-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-3-methyl[1,1'-biphenyl]-4-carboxamide



The titled compound (129 mg) was obtained as a white powder by the same method as in Example 16, using 4-bromo-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-2-methylbenzamide (250 mg, 0.623 mmol) obtained in Example 24, and 4-chlorophenylboric acid (117 mg, 0.747 mmol).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.42 (1H, m), 1.96 (2H, m), 2.37 (6H, s), 2.37-2.47 (3H, m), 2.56 (3H, s), 2.90 (3H, m), 7.08 (1H, d, $J=8.1$ Hz), 7.26 (1H, m), 7.41 (6H, m), 7.53 (3H, m).

Elemental analysis for $\text{C}_{27}\text{H}_{29}\text{ClN}_2\text{O} \cdot \text{H}_2\text{O}$

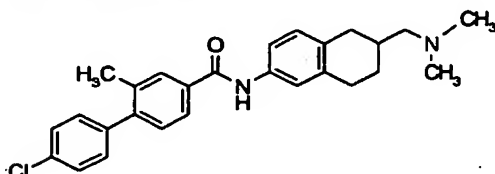
Calcd.: C, 71.90; H, 6.93; N, 6.21.

Found: C, 71.92; H, 6.52; N, 5.92.

Melting point: 163 - 165°C (crystallization solvent: ethyl acetate-diethyl ether)

Example 28

4'-Chloro-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-2-methyl[1,1'-biphenyl]-4-carboxamide



The titled compound (168 mg) was obtained as a white powder by the same method as in Example 16, using 4-bromo-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-3-methylbenzamide (250 mg, 0.623 mmol) obtained in Example 25, and 4-chlorophenylboric acid (117 mg, 0.747 mmol).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.41 (1H, m), 1.95 (2H, m), 2.26 (6H, s), 2.24-2.42 (3H, m), 2.33 (3H, s), 2.85 (3H, m), 7.09 (1H, d, $J=8.4$ Hz), 7.26 (4H, m), 7.43 (3H, m), 7.73 (3H, m).

Elemental analysis for $\text{C}_{27}\text{H}_{29}\text{ClN}_2\text{O} \cdot 0.2\text{H}_2\text{O}$

Calcd.: C, 74.28; H, 6.79; N, 6.42.

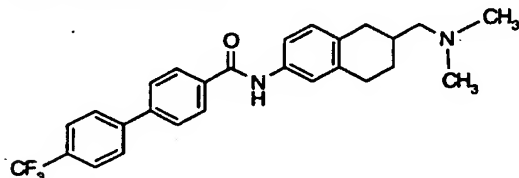
Found: C, 74.27; H, 6.73; N, 6.27.

Melting point: 193 - 195°C (crystallization solvent: ethyl

acetate-diethyl ether)

Example 29

5 N-[6-[(N,N-Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4'-(trifluoromethyl)[1,1-biphenyl]-4-carboxamide



The titled compound (194 mg) was obtained as a white powder by the same method as in Example 16, using 4-bromo-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]benzamide (250 mg, 0.645 mmol) obtained in Example 15, and 4-trifluoromethylphenylboric acid (147 mg, 0.775 mmol).

¹H-NMR (CDCl₃) δ: 1.41 (1H, m), 1.95 (2H, m), 2.25 (6H, s), 2.25-2.45 (3H, m), 2.89 (3H, m), 7.09 (1H, d, J=8.1 Hz), 7.31 (1H, d, J=8.1 Hz), 7.46 (1H, s), 7.70 (6H, m), 7.80 (1H, m), 7.96 (2H, d, J=8.4 Hz).

Elemental analysis for C₂₇H₂₇F₃N₂O

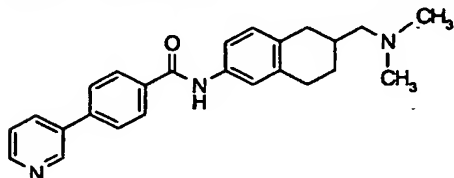
Calcd.: C, 71.66; H, 6.01; N, 6.19.

20 Found: C, 71.44; H, 6.05; N, 6.09.

Melting point: 205 - 206°C (crystallization solvent: ethyl acetate-diisopropyl ether).

Example 30

25 N-[6-[(N,N-Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4-(3-pyridinyl)benzamide



The titled compound (194 mg) was obtained as a white powder by the same method as in Example 16, using 4-bromo-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-

30

tetrahydro-2-naphthalenyl)benzamide (250 mg, 0.645 mmol) obtained in Example 15, and 2-(3-pyridyl)-1,3,2,-dioxaborinane (126 mg, 0.775 mmol).

¹H-NMR (CDCl₃) δ: 1.41 (1H, m), 1.95 (2H, m), 2.26 (6H, s),
 5 2.26-2.42 (3H, m), 2.85 (3H, m), 7.09 (1H, d, J=7.8 Hz),
 7.30-7.47 (3H, m), 7.69 (2H, d, J=8.4 Hz), 7.86-7.99 (4H, m), 8.64 (1H, m), 8.87 (1H, m).

Elemental analysis for C₂₅H₂₇N₃O · 0.1H₂O

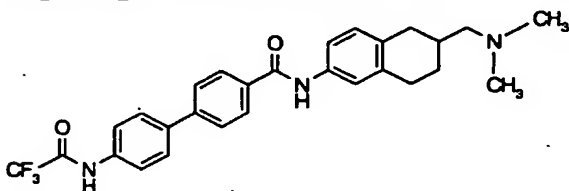
Calcd.: C, 77.53; H, 7.08; N, 10.85.

10 Found: C, 77.42; H, 7.05; N, 10.58.

Melting point: 177 - 178°C (crystallization solvent: ethyl acetate-diisopropyl ether)

Example 31

15 N-[6-[(N,N-Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4'-[(trifluoroacetyl)amino][1,1'-biphenyl]-4-carboxamide



The titled compound (1.02 g) was obtained as a white
 20 powder by the same method as in Example 16, using 4-bromo-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]benzamide (1.00 g, 2.58 mmol) obtained in Example 15, and 4-trifluoroacetamidophenylboric acid (722 mg, 3.10 mmol).
 25 ¹H-NMR (CDCl₃) δ: 1.41 (1H, m), 2.05 (2H, m), 2.26 (6H, s),
 2.26-2.42 (3H, m), 2.89 (3H, m), 7.09 (1H, d, J=8.4 Hz),
 7.29 (2H, m), 7.46 (1H, s), 7.69 (7H, m), 7.94 (2H, d, J=8.1 Hz).

Elemental analysis for C₂₈H₂₈F₃N₃O₂

30 Calcd.: C, 67.87; H, 5.70; N, 8.48.

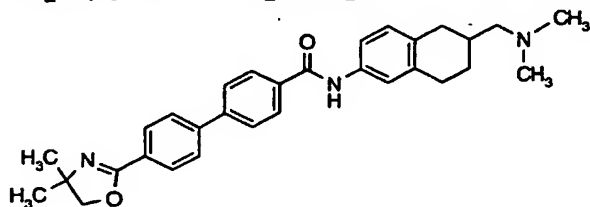
Found: C, 67.70; H, 5.53; N, 8.42.

Melting point: 235 - 237°C (crystallization solvent: ethyl

acetate-diisopropyl ether)

Example 32

N-[6-[(N,N-Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4'-(4,4-dimethyl-4,5-dihydro-1,3-oxazole-2-yl)[1,1'-biphenyl]-4-carboxamide



The titled compound (238 mg) was obtained as a white powder by the same method as in Example 16, using 4-bromo-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]benzamide (250 mg, 0.645 mmol) obtained in Example 15, and 4-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)phenylboronic acid (170 mg, 0.775 mmol).

¹H-NMR (CDCl₃) δ: 1.41 (7H, m), 1.94 (2H, m), 2.25 (6H, s), 2.25-2.41 (3H, m), 2.84 (3H, m), 4.14 (2H, s), 7.08 (1H, d, J=7.8 Hz), 7.30 (1H, m), 7.46 (1H, s), 7.68 (5H, m), 7.94 (2H, d, J=8.4 Hz), 8.03 (2H, d, J=8.4 Hz).

Elemental analysis for C₃₁H₃₅N₃O₂ · 0.2H₂O

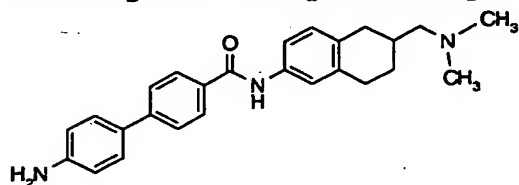
Calcd.: C, 76.74; H, 7.35; N, 8.66.

Found: C, 76.70; H, 7.19; N, 8.49.

Melting point: 185 - 187°C (crystallization solvent: ethyl acetate-diisopropyl ether)

Example 33

4'-Amino-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



N-[6-[(N,N-Dimethylamino)methyl]-5,6,7,8-

tetrahydro-2-naphthalenyl]-4'-

[(trifluoroacetyl)amino][1,1'-biphenyl]-4-carboxamide
(850 mg, 1.72 mmol) obtained in Example 31 was suspended
in a mixed solution of methanol (8 ml) and tetrahydrofuran
(4 ml), then 1N sodium hydroxide (3.4 ml) was added, which
was stirred at 50° C for 16 hours. The solvent was distilled
out under reduced pressure, and the residue was pulverized
using water, to give the titled compound (685 mg) as a white
powder.

¹H-NMR (CDCl₃) δ: 1.31 (1H, m), 1.89 (2H, m), 2.15 (6H, s),
2.15-2.34 (3H, m), 2.83 (3H, m), 5.36 (2H, s), 6.67 (2H,
d, J=8.4 Hz), 7.03 (1H, d, J=8.1 Hz), 7.48 (4H, m), 7.68
(2H, d, J=8.1 Hz), 7.96 (2H, d, J=8.4 Hz), 10.02 (1H, s).
Elemental analysis for C₂₆H₂₉N₃O · 1.1H₂O

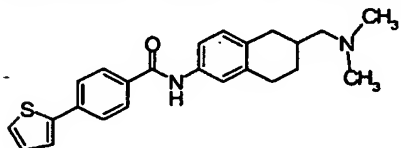
Calcd.: C, 74.47; H, 7.50; N, 10.02.

Found: C, 74.39; H, 7.41; N, 9.82.

Melting point: 148 - 150° C (crystallization solvent:
methanol-water)

Example 34

N-[6-[(N,N-Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-
naphthalenyl]-4-(2-thienyl) benzamide



The titled compound (70 mg) was obtained as a white
powder by the same method as in Example 16, using 4-
bromo-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-
tetrahydro-2-naphthalenyl]benzamide (250 mg, 0.645 mmol)
obtained in Example 15, and 2-thienylboric acid (99.1 mg,
0.775 mmol).

¹H-NMR (CDCl₃) δ: 1.41 (1H, m), 1.94 (2H, m), 2.25 (6H, s),
2.25-2.45 (3H, m), 2.89 (3H, m), 7.11 (2H, m), 7.29-7.45
(4H, m), 7.71 (3H, m), 7.87 (2H, d, J=8.4 Hz).

Elemental analysis for C₂₄H₂₆N₂OS

Calcd.: C, 73.81; H, 6.71; N, 7.17.

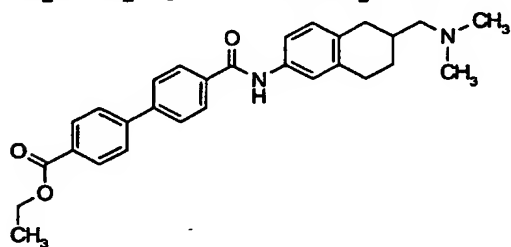
Found: C, 73.49; H, 6.59; N, 7.14.

Melting point: 165 - 166°C (crystallization solvent: ethyl acetate-diisopropyl ether)

5

Example 35

Ethyl 4'-[[[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]amino]carbonyl][1,1'-biphenyl]-4-carboxylate



10

The titled compound (202 mg) was obtained as a white powder by the same method as in Example 16, using 4-bromo-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]benzamide (250 mg, 0.645 mmol) obtained in Example 15, and 4-ethoxycarbonylphenylboric acid (150 mg, 0.775 mmol).

15

¹H-NMR (CDCl₃) δ: 1.42 (4H, m), 1.95 (2H, m), 2.26 (6H, s), 2.26-2.42 (3H, m), 2.89 (3H, m), 4.41 (2H, q, J=7.2 Hz), 7.09 (1H, d, J=8.4 Hz), 7.31 (1H, d, J=8.4 Hz), 7.47 (1H, s), 7.70 (4H, m), 7.80 (1H, s), 7.96 (2H, d, J=8.4 Hz), 8.14 (2H, d, J=8.4 Hz).

20

Elemental analysis for C₂₉H₃₂N₂O₃

Calcd.: C, 76.29; H, 7.06; N, 6.14.

Found: C, 76.25; H, 7.07; N, 6.09.

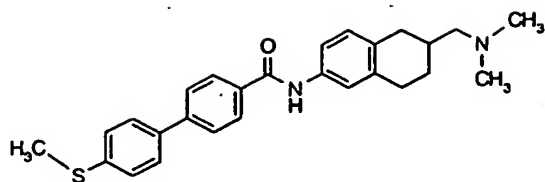
25

Melting point: 156 - 158°C (crystallization solvent: ethyl acetate-diisopropyl ether)

Example 36

N-[6-[(N,N-Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4'-(methylsulfanyl)[1,1'-biphenyl]-4-carboxamide

30



The titled compound (360 mg) was obtained as a white powder by the same method as in Example 16, using 4-bromo-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]benzamide (500 mg, 1.29 mmol) obtained in Example 15, and 4-methylthiophenylboric acid (260 mg, 1.55 mmol).

¹H-NMR (CDCl₃) δ: 1.41 (1H, m), 1.94 (2H, m), 2.26 (6H, s), 2.26-2.42 (3H, m), 2.53 (3H, s), 2.94 (3H, m), 7.09 (1H, d, J=8.1 Hz), 7.29-7.36 (3H, m), 7.46 (1H, s), 7.56 (2H, d, J=8.4 Hz), 7.67 (2H, d, J=8.1 Hz), 7.78 (1H, m), 7.92 (2H, d, J=9.0 Hz).

Elemental analysis for C₂₇H₃₀N₂OS · 0.2H₂O

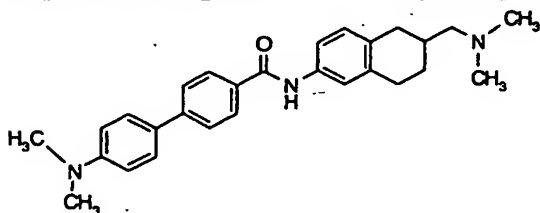
Calcd.: C, 74.69; H, 7.04; N, 6.45.

Found: C, 74.63; H, 7.03; N, 6.11.

Melting point: 178 - 180°C (crystallization solvent: ethyl acetate-diisopropyl ether)

Example 37

4'-(N,N-Dimethylamino)-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



4'-Amino-N-[6-[(N,N-dimethyl)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide (150 mg, 0.375 mmol) obtained in Example 33, and paraformaldehyde (45.1 mg, 1.50 mmol) were suspended in mixed solution of methanol (1 ml) and tetrahydrofuran (1 ml). Sodium cyanohydroborate (94.4 mg, 1.50 mmol) was

added to the reaction mixture, which was stirred at 40°C for 18 hours. Ethyl acetate was added to the reaction mixture, which was washed with saturated aqueous sodium chloride solution, dried using anhydrous magnesium sulfate, and the solvent was distilled out under reduced pressure. The residue was refined using alumina column chromatography (development solvent; ethyl acetate), and pulverized using isopropyl ether, to give the titled compound (13 mg) as a white powder.

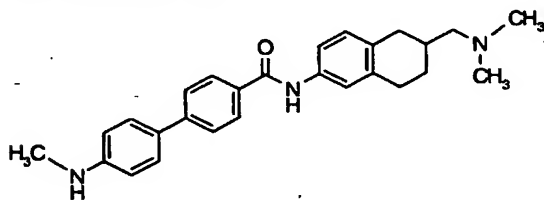
¹H-NMR (DMSO-d₆) δ: 1.32 (1H, m), 1.90 (2H, m), 2.15 (6H, s), 2.15-2.35 (3H, m), 2.77 (3H, m), 2.97 (6H, s), 6.82 (2H, d, J=8.4 Hz), 7.03 (1H, d, J=8.4 Hz), 7.48 (1H, d, J=8.1 Hz), 7.53 (1H, s), 7.63 (2H, d, J=8.7 Hz), 7.74 (2H, d, J=7.8 Hz), 7.98 (2H, d, J=8.4 Hz), 10.04 (1H, s).

FABMS(pos) 428.2[M+H]⁺

Melting point: 212 - 213°C (crystallization solvent: ethyl acetate-diisopropyl ether)

Example 38

N-[6-[(N,N-Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4'-(methylamino)[1,1'-biphenyl]-4-carboxamide



The titled compound was obtained as a white powder by the same method as in Example 37, using 4'-amino-N-[6-[(N,N-dimethyl)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl] [1,1'-biphenyl]-4-carboxamide (150 mg, 0.375 mmol) obtained in Example 33, paraformaldehyde (15.0 mg, 0.50 mmol), and sodium cyanohydroborate (31.5 mg, 0.50 mmol).

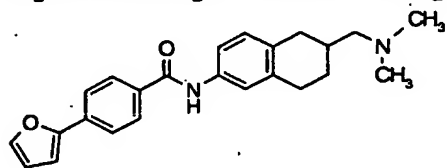
¹H-NMR (DMSO-d₆) δ: 1.32 (1H, m), 1.89 (2H, m), 2.15 (6H, s), 2.15-2.31 (3H, m), 2.72 (7H, m), 5.94 (1H, m), 6.64 (2H,

d, J=9.0 Hz), 7.03 (1H, d, J=8.7 Hz), 7.49 (4H, m), 7.70 (1H, d, J=8.4 Hz), 7.97 (2H, d, J=8.4 Hz), 10.02 (1H, s).
FABMS(pos) 414.3[M+H]⁺

Melting point: 163 - 165°C (crystallization solvent: ethyl acetate-diisopropyl ether)

Example 39

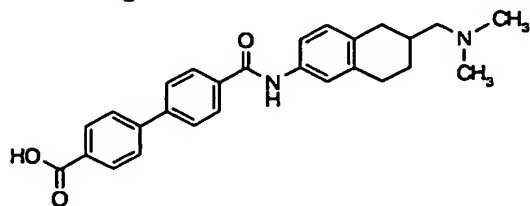
N-[6-[(N,N-Dimethyl)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4-(2-furyl)benzamide



The titled compound (67 mg) was obtained as a white powder by the same method as in Example 16, using 4-bromo-N-[6-[(N,N-dimethyl)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]benzamide (250 mg, 0.645 mmol) obtained in Example 15, and 2-furylboric acid (86.7 mg, 0.775 mmol).
¹H-NMR (DMSO-d₆) δ: 1.40 (1H, m), 1.94 (2H, m), 2.25 (6H, s), 2.25-2.45 (3H, m), 2.88 (3H, m), 7.08 (1H, d, J=8.1 Hz), 7.26 (4H, m), 7.41 (1H, m), 7.60-7.74 (5H, m).
FABMS(pos) 375.2[M+H]⁺

Example 40

4'-[[[6-[(N,N-Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]amino]carbonyl][1,1'-biphenyl]-4-carboxylic acid



Ethyl-4'-[[[6-[(N,N-dimethyl)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]amino]carbonyl][1,1'-biphenyl]-4-carboxylate (100 mg, 0.219 mmol) obtained in Example 35 was dissolved in a mixed solution of ethanol (3

ml) and water (0.5 ml). 1N aqueous sodium hydroxide solution (0.329 ml) was added to the reaction mixture at room temperature, which was stirred at 90°C for 5 hours.

After the solvent was distilled out under reduced pressure, water was added to the residue, then 1N hydrochloric acid (0.329 ml) was added and the reaction mixture was stirred. The precipitated crude product collected by filtration, and washed with water to give the titled compound (89 mg) as a white powder.

¹H-NMR (DMSO-d₆) δ: 1.34 (1H, m), 1.91 (2H, m), 2.24 (6H, s), 2.24-2.30 (3H, m), 2.81 (3H, m), 7.05 (1H, d, J=8.4 Hz), 7.49 (1H, d, J=8.4 Hz), 7.55 (1H, s), 7.89 (4H, m), 8.07 (4H, m), 10.18 (1H, s).

Elemental analysis for C₂₇H₂₈N₂O₃ · 2H₂O

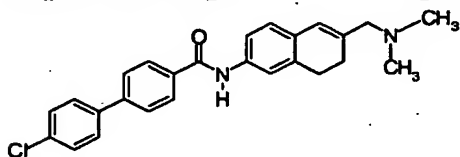
Calcd.: C, 69.81; H, 6.94; N, 6.03.

Found: C, 69.57; H, 7.01; N, 5.93.

Melting point: 143°C (decomposition) (crystallization solvent: water)

Example 41

4'-Chloro-N-[6-[(N,N-dimethyl)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



1) 6-Acetamido-1-tetralone (5.0 g, 0.0246 mol) synthesized according to a known method by documents (Journal of Organic Chemistry 27, 70 (1962)), was dissolved in 50 ml of DMF dimethylacetal, which was stirred at 110°C for 2 hours. The precipitate was collected by filtration, and washed with ethyl acetate to give 6-acetamido-2-(N,N-dimethylaminomethylidene)-1-tetralone (4.98 g) as a yellow powder.

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.79-2.83 (2H, m), 2.88-

2.92 (2H, m), 3.11 (6H, s), 7.14-7.17 (1H, m), 7.68 (1H, s), 7.69 (1H, s), 7.95 (1H, d, J=8.1Hz), 7.96 (1H, s).

Melting point: 207 - 210°C (crystallization solvent: ethyl acetate)

- 5 2) The obtained 6-acetamido-2-(N,N-dimethylaminomethylidene)-1-tetralone (4.50 g, 0.0173 mol) was dissolved in methanol (50 ml), and sodium borohydride (6.56 g, 0.173 mol) was added to the solution under ice-cooling, which was stirred for 2 hours. The
- 10 reaction mixture was concentrated. Ethyl acetate and sodium hydrogencarbonate solution were added to the residue, and extraction was conducted. The ethyl acetate layer was concentrated, and 30 ml of tetrahydrofuran and 30 ml of 2N hydrochloric acid were added to the residue,
- 15 which was refluxed with heating for 16 hours. The reaction mixture was concentrated, and ethyl acetate and 2N sodium hydroxide solution were added, and extraction was conducted. The ethyl acetate layer was concentrated, and the residue was refined using alumina column chromatography
- 20 (development solvent; ethyl acetate:n-hexane = 30:70), to give 6-[(N,N-dimethylamino)methyl]-7,8-dihydro-2-naphthaleneamine (1.60 g) as a colorless oily substance.
- 25 ¹H-NMR (CDCl₃) δ: 2.23 (6H, s), 2.28 (2H, t, J=8.4Hz), 2.74 (2H, t, J=8.4Hz), 2.95 (2H, s), 3.57-3.72 (2H, m), 6.25 (1H, s), 6.46-6.48 (2H, m), 6.83 (1H, d, J=8.7Hz).

- 3) The titled compound (1.12 g) was obtained as a white powder by the same method as in Example 1, using the obtained 6-[(N,N-dimethylamino)methyl]-7,8-dihydro-2-naphthalenamine (1.00 g, 0.005 mol), and 4-chlorobiphenyl
- 30 carboxylic acid (2.31 g, 0.01 mol).
- ¹H-NMR (CDCl₃) δ: 2.25 (6H, s), 2.34 (2H, t, J=7.8Hz), 2.86 (2H, t, J=7.8Hz), 2.99 (2H, s), 6.34 (1H, s), 7.03 (1H, d, J=8.7Hz), 7.39 (1H, d, J=8.1 Hz), 7.45 (2H, d, J=8.7), 7.48 (1H, s), 7.56 (2H, d, J=8.4 Hz), 7.67 (2H, d, J=8.4 Hz),
- 35 7.78 (1H, s), 7.94 (2H, d, J=8.4 Hz).

Elemental analysis for C₂₆H₂₅ClN₂O

Calcd.: C, 74.90; H, 6.04; N, 6.72.

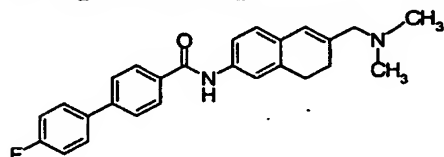
Found: C, 74.64; H, 6.14; N, 6.56.

Melting point: 204 - 207°C (crystallization solvent: ethyl acetate - n-hexane)

5

Example 42

4'-Fluoro-N-[6-[(N,N-dimethylamino)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



10 The titled compound (990 mg) was obtained as a white powder by the same method as in Example 1, using 6-[(N,N-dimethylamino)methyl]-7,8-dihydro-2-naphthalenamine (936 mg, 4.62 mmol) obtained in Example 41-2), and 4-fluorobiphenylcarboxylic acid (1.00 g, 4.62 mmol).

15 ¹H-NMR (CDCl₃) δ: 2.25 (6H, s), 2.34 (2H, t, J=8.1Hz), 2.85 (2H, t, J=8.1Hz), 2.99 (2H, s), 6.34 (1H, s), 7.02 (1H, d, J=8.1Hz), 7.13-7.19 (2H, m), 7.38-7.41 (1H, m), 7.48 (1H, s), 7.56-7.61 (2H, m), 7.65 (2H, d, J=8.4 Hz), 7.80 (1H, s), 7.93 (2H, d, J=8.5Hz).

20

Elemental analysis for C₂₆H₂₅N₂O

Calcd.: C, 77.97; H, 6.29; N, 6.99.

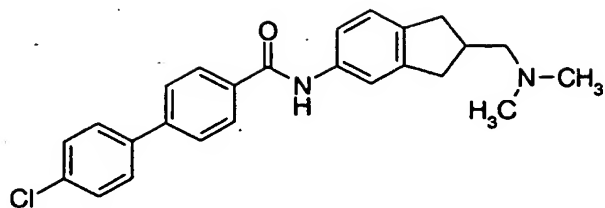
Found: C, 77.90; H, 6.23; N, 6.58.

Melting point: 190 - 193°C (crystallization solvent: ethyl acetate - n-hexane)

25

Example 43

4'-Chloro-N-[2-[(dimethylamino)methyl]-2,3-dihydro-1H-inden-5-yl][1,1'-biphenyl]-4-carboxamide



Concentrated hydrochloric acid (1 ml) was added to N-[2-[(dimethylamino)methyl]-2,3-dihydro-1H-inden-5-yl]acetamide (48.9 mg, 0.210 mmol) obtained in Reference Example 48, which was stirred at 110°C for 2 hours, and the solvent was distilled out under reduced pressure. Ethyl acetate was added to the residue, which was washed with potassium carbonate solution and saturated aqueous sodium chloride solution, dried using anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. Using the oily substance obtained, the same operation as in Example 1 was conducted to give the titled compound (30 mg).

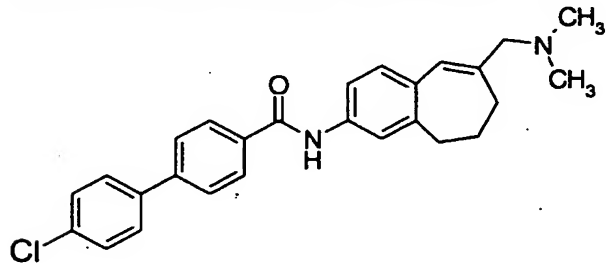
¹H NMR (DMSO-d₆) δ: 2.16 (6H, s), 2.22 (2H, d, J = 6.7 Hz), 2.61 (4H, m), 2.97 (1H, m), 7.15 (1H, d, J = 8.1 Hz), 7.47 (1H, d, J = 8.1 Hz), 7.56 (2H, d, J = 8.4 Hz), 8.05 (2H, d, J = 8.4 Hz), 10.17 (1H, s).

FAB(pos) 405.1 [M+H]⁺

Melting point: 192 - 194°C (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 44

4'-Chloro-N-[8-[(dimethylamino)methyl]-6,7-dihydro-5H-benzo[a]cyclohepten-3-yl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 8-

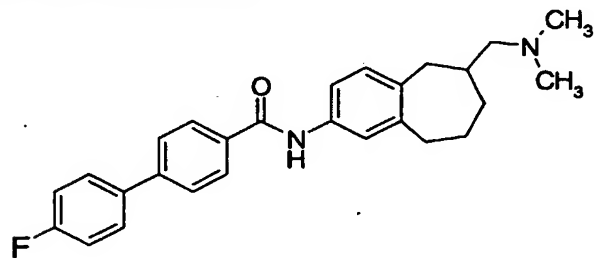
[(dimethylamino)methyl]-6,7-dihydro-5H-benzo[a]cyclohepten-3-amine obtained in Reference Example 50.

¹H-NMR (CDCl₃) δ: 1.96-2.10 (2H, m), 2.25 (6H, s), 2.39 (2H, t, J = 6.4 Hz), 2.79-2.85 (2H, m), 2.96 (2H, s), 6.40 (1H, s), 7.15 (1H, d, J = 8.6 Hz), 7.40-7.52 (4H, m), 7.56 (2H, d, J = 8.4 Hz), 7.67 (2H, d, J = 8.1 Hz), 7.81 (1H, s), 7.94 (2H, d, J = 8.1 Hz).

Melting point: 183-185°C (crystallization solvent: ethyl acetate - diethyl ether)

Example 45

4'-Fluoro-N-[6-[(dimethylamino)methyl]-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-2-yl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-[(dimethylamino)methyl]-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-2-amine obtained in Reference Example 51.

¹H-NMR (CDCl₃) δ: 1.40-1.68 (3H, m), 1.85-2.20 (10H, m), 2.55-2.92 (4H, m), 7.13-7.20 (3H, m), 7.35-7.43 (2H, m), 7.56-7.67 (4H, m), 7.77 (1H, s), 7.93 (2H, d, J=8.4 Hz).

Elemental analysis for C₂₇H₂₉FN₂O

Calcd.: C, 77.85; H, 7.02; N, 6.73.

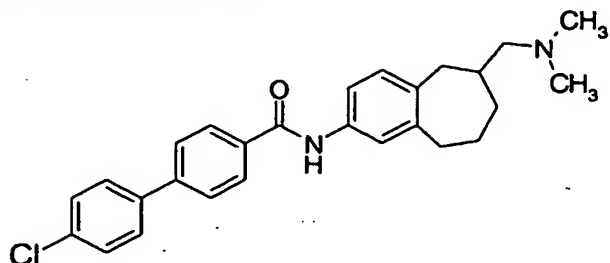
Found: C, 78.18; H, 7.09; N, 6.74.

Melting point: 167 - 169°C (crystallization solvent: diethyl ether)

Example 46

4'-Chloro-N-[6-[(dimethylamino)methyl]-6,7,8,9-

tetrahydro-5H-benzo[a]cyclohepten-2-yl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Experiment Example 1, using 6-[(dimethylamino)methyl]-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-2-amine obtained in Reference Example 51.

¹H-NMR (CDCl₃) δ: 1.40-1.67 (3H, m), 1.85-2.20 (10H, m), 2.55-2.92 (4H, m), 7.15 (1H, d, J = 8.1 Hz), 7.35-7.46 (4H, m), 7.56 (2H, d, J = 8.4 Hz), 7.66 (2H, d, J = 8.1 Hz), 7.77 (1H, s), 7.93 (2H, d, J = 8.4 Hz).

Elemental analysis for C₂₇H₂₉ClN₂O

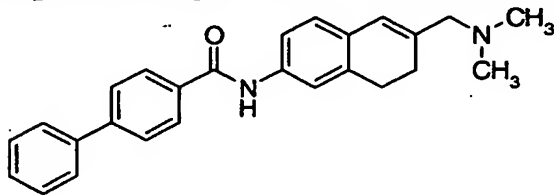
Calcd.: C, 74.90; H, 6.75; N, 6.47.

Found: C, 74.77; H, 6.65; N, 6.43.

Melting point: 173 - 175°C (crystallization solvent: diethyl ether)

Example 47

N-[6-[(Dimethylamino)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-[(N,N-dimethylamino)methyl]-7,8-dihydro-2-naphthalenamine obtained in Example 41-2).

¹H NMR (CDCl₃) δ: 2.25 (6H, s), 2.33 (2H, t, J = 5.4 Hz),

2.84 (2H, t, $J = 5.4$ Hz), 2.98 (2H, s), 6.34 (1H, s), 7.01 (1H, d, $J = 7.8$ Hz), 7.32-7.94 (12H, m).

Elemental analysis for $C_{26}H_{26}N_2O$

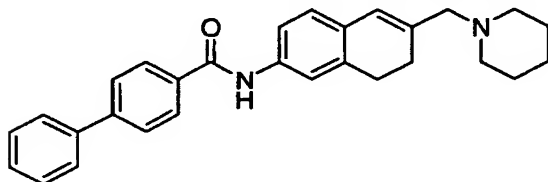
Calcd.: C, 81.64; H, 6.85; N, 7.32.

5 Found: C, 81.65; H, 6.79; N, 6.91.

Melting point: 173 - 175°C (crystallization solvent: tetrahydrofuran - n-hexane)

Example 48

10 N-[6-(1-Piperidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(1-piperidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 52.

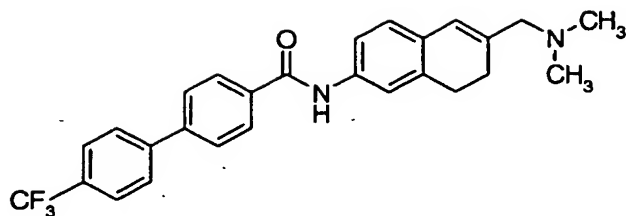
^1H NMR (CDCl_3) δ : 1.46-1.59 (6H, m), 2.31-2.36 (6H, m), 2.84 (2H, t, $J = 8.0$ Hz), 3.02 (2H, s), 6.34 (1H, s), 7.02 (1H, d, $J = 8.1$ Hz), 7.37-7.50 (4H, m), 7.63 (2H, d, $J = 6.9$ Hz), 7.71 (2H, d, $J = 8.1$ Hz), 7.79 (1H, s), 7.94 (2H, d, $J = 8.1$ Hz).

Melting point: 156 - 158°C (crystallization solvent: tetrahydrofuran - n-hexane)

25 Example 49

N-[6-[(Dimethylamino)methyl]-7,8-dihydro-2-naphthalenyl]-4'-trifluoromethyl[1,1'-biphenyl]-4-carboxamide

197.



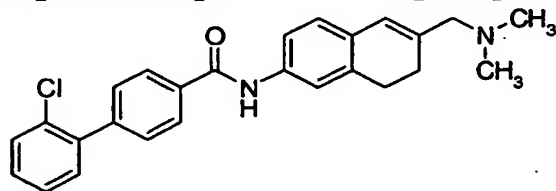
The titled compound was obtained by carrying out the same operation as in Example 1, using 6-[(N,N-dimethylamino)methyl]-7,8-dihydro-2-naphthalenamine
 5 obtained in Example 41-2).

¹H NMR (CDCl₃) δ: 2.25 (6H, s), 2.34 (d, J = 5.1 Hz), 2.86 (2H, d, J = 5.1 Hz), 2.99 (2H, s), 6.35 (1H, s), 7.04 (1H, d, J = 8.4 Hz), 7.40 (1H, d, J = 3.3 Hz), 7.49 (1H, s), 7.70-7.79 (6H, m), 7.87 (2H, d, J = 8.4 Hz).

10 Melting point: 214 - 216°C (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 50

2'-Chloro-N-[6-[(dimethylamino)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide
 15



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-[(N,N-dimethylamino)methyl]-7,8-dihydro-2-naphthalenamine
 20 obtained in Example 41-2).

¹H NMR (CDCl₃) δ: 2.25 (6H, s), 2.34 (d, J = 5.1 Hz), 2.85 (2H, d, J = 5.1 Hz), 3.00 (2H, s), 6.34 (1H, s), 6.69 (1H, s), 7.02 (1H, d, J = 8.4 Hz), 7.31-7.57 (8H, m), 7.85 (1H, s), 7.92 (2H, d, J = 7.8 Hz).

25 Elemental analysis for C₂₆H₂₅ClN₂O

Calcd.: C, 74.90; H, 6.04; N, 6.72

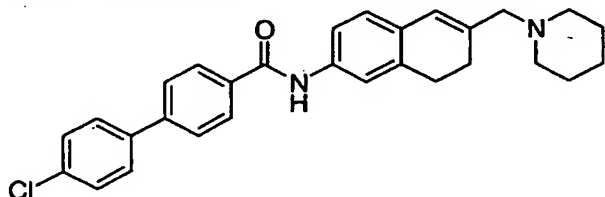
Found: C, 74.49; H, 5.65; N, 6.06.

Melting point: 145 - 147°C (crystallization solvent: ethyl

acetate - n-hexane)

Example 51

4'-Chloro-N-[6-(1-piperidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



After N,N-dimethylformaldehyde solution (5 ml) of 4'-chloro-N-[6-(chloromethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide (225 mg) obtained in Reference Example 56, piperidine (0.16 ml), and diisopropylethylamine (0.282 ml) was stirred at room temperature for 15 hours, which was heated at 120°C for 2 hours. The residue obtained by concentrating the reaction mixture was dissolved in water-ethyl acetate, then extracted using ethyl acetate. The extract was washed with saturated aqueous sodium chloride solution, dried using anhydrous magnesium sulfate, and then the solvent was distilled out under reduced pressure. The resulting residue was refined using alumina column chromatography (development solvent; tetrahydrofuran:n-hexane = 1:5), and crystallized using tetrahydrofuran - n-hexane to give the titled compound (110 mg).

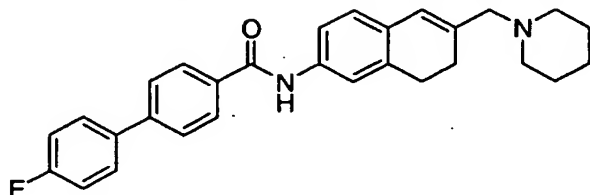
¹H NMR (CDCl₃) δ: 1.26-1.61 (6H, m), 2.30-2.36 (6H, m), 2.83 (2H, t, J = 8.4 Hz), 3.02 (2H, s), 6.33 (1H, s), 7.01 (1H, d, J = 8.1 Hz), 7.36-7.49 (4H, m), 7.55 (2H, d, J = 8.4 Hz), 7.66 (2H, d, J = 8.4 Hz), 7.81 (1H, s), 7.93 (2H, d, J = 8.1 Hz).

Melting point: 209 - 211°C (crystallization solvent: tetrahydrofuran - n-hexane)

Example 52

4'-Fluoro-N-[6-(1-piperidinylmethyl)-7,8-dihydro-2-

naphthalenyl][1,1'-biphenyl]4-carboxamide



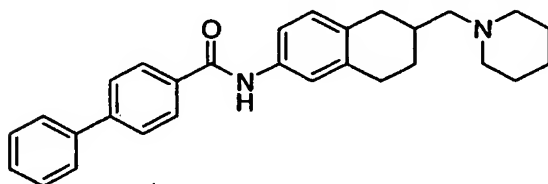
The titled compound was obtained by carrying out the same operation as in Example 1, using the 6-(1-piperidinylmethyl)-7,8-dihydro-2-naphthalene amine obtained in Reference example 52.

^1H NMR (CDCl_3) δ : 1.45-1.58 (6H, m), 2.29-2.37 (6H, m), 2.82 (2H, t, $J = 8.0$ Hz), 3.01 (2H, s), 6.33 (1H, s), 6.98-7.93 (12H, m).

Melting point: 190 - 192°C (crystallization solvent: tetrahydrofuran - n-hexane)

Example 53

N-[6-(1-Piperidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(1-piperidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenamine obtained in Reference Example 53.

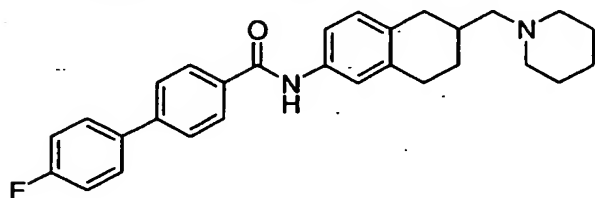
^1H NMR (CDCl_3) δ : 1.37-1.60 (8H, m), 1.96-2.00 (2H, m), 2.24-2.44 (5H, m), 2.82-2.93 (3H, m), 7.09 (1H, d, $J = 8.3$ Hz), 7.30-7.33 (1H, m), 7.38-7.65 (6H, m), 7.70 (2H, d, $J = 8.4$ Hz), 7.76 (1H, s), 7.93 (2H, d, $J = 8.4$ Hz).

Melting point: 160 - 162°C (crystallization solvent: tetrahydrofuran - n-hexane)

Example 54

4'-Fluoro-N-[6-(1-piperidinylmethyl)-5,6,7,8-

tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(1-piperidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenamine obtained in Reference Example 53.

^1H NMR (CDCl_3) δ : 1.36-1.52 (8H, m), 2.29-2.31 (2H, m), 2.24-2.45 (6H, m), 2.82-2.93 (3H, m), 7.08-7.33 (4H, m), 7.44 (1H, s), 7.57-7.66 (4H, m), 7.74 (1H, s), 7.92 (2H, J = 8.1 Hz).

Elemental analysis for $\text{C}_{29}\text{H}_{31}\text{FN}_2\text{O}$

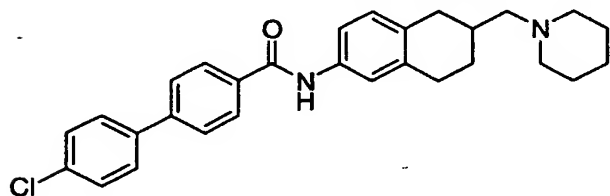
Calcd.: C, 78.70; H, 7.08; N, 6.33.

Found: C, 78.40; H, 7.09; N, 6.09.

Melting point: 179 - 181°C (crystallization solvent: ethyl acetate)

Example 55

4'-Chloro-N-[6-(1-piperidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



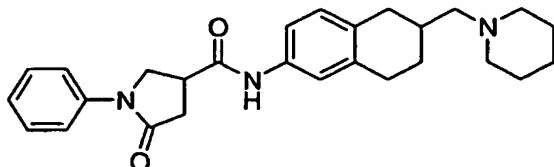
The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(1-piperidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenamine obtained in Reference Example 53.

^1H NMR (CDCl_3) δ : 1.25-1.71 (8H, m), 1.95-2.00 (2H, m), 2.25-2.45 (6H, m), 2.83-2.93 (3H, m), 7.09 (1H, d, J = 8.3 Hz), 7.30-7.32 (1H, m), 7.43-7.45 (3H, m), 7.55 (2H, d, J = 8.1 Hz), 7.65 (2H, d, J = 8.4 Hz), 7.77 (1H, s), 7.93 (2H, d, J = 8.1 Hz).

Melting point: 202 - 203°C (crystallization solvent:
tetrahydrofuran - n-hexane)

Example 56

- 5 5-Oxo-1-phenyl-N-[6-(1-piperidinylmethyl)-5,6,7,8-
tetrahydro-2-naphthalenyl]-3-pyrrolidinecarboxamide



- The titled compound was obtained by carrying out the
same operation as in Example 1, using 6-(1-
10 piperidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenamine
obtained in Reference Example 53.

^1H NMR (CDCl_3) δ : 1.03-3.33 (22H, m), 3.97 (1H, t, J = 8.4
Hz), 4.21 (1H, dd, J = 6.8, 7.1 Hz), 6.91-7.63 (9H, m).

Elemental analysis for $\text{C}_{27}\text{H}_{33}\text{N}_3\text{O}_2$

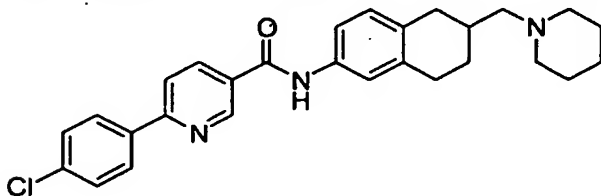
- 15 Calcd.: C, 75.14; H, 7.71; N, 9.74.

Found: C, 75.01; H, 7.33; N, 9.43.

Melting point: 162 - 164°C (crystallization solvent: ethyl
acetate)

- 20 Example 57

6-(4-Chlorophenyl)-N-[6-(1-piperidinylmethyl)-5,6,7,8-
tetrahydro-2-naphthalenyl]nicotinamide



- The titled compound was obtained by carrying out the
same operation as in Example 1, using 6-(1-
25 piperidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenamine
obtained in Reference Example 53.

^1H NMR (CDCl_3) δ : 1.30-2.40 (16H, m), 2.82-2.92 (3H, m),
7.09 (1H, d, J = 8.1 Hz), 7.26-7.48 (4H, m), 7.80 (2H, d,

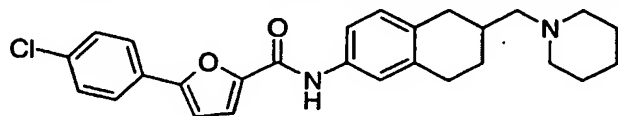
$J = 8.7$ Hz), 7.99 (2H, d, $J = 8.7$ Hz), 8.23 (d, 1H, $J = 6.3$ Hz), 9.11 (1H, s).

Melting point: 193 - 195°C (crystallization solvent: ethyl acetate)

5

Example 58

5-(4-Chlorophenyl)-N-[6-(1-piperidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenyl]-2-furamide

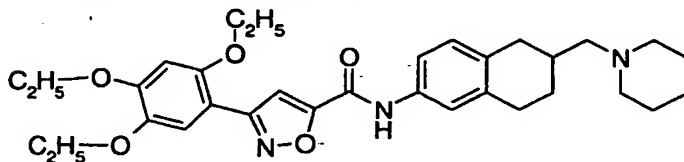


10 The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(1-piperidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenamine obtained in Reference Example 53.

^1H NMR (CDCl_3) δ : 1.23-1.61 (7H, m), 1.96-2.00 (2H, m),
15 2.24-2.43 (7H, m), 2.80-2.92 (3H, m), 6.75 (1H, d, $J = 3.6$ Hz), 7.07 (1H, d, $J = 8.4$ Hz), 7.27 (1H, d, $J = 3.6$ Hz), 7.32-7.42 (4H, m), 7.66 (2H, d, $J = 8.4$ Hz), 8.32 (1H, s).

Example 59

20 N-[6-(1-Piperidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenyl]-3-(2,4,5-triethoxyphenyl)-5-isoxazolecarboxamide

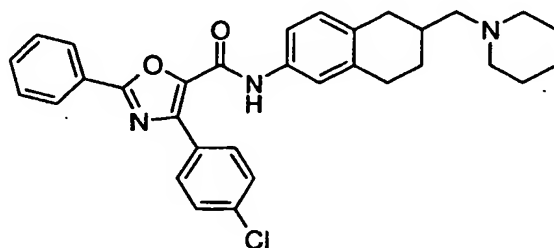


25 The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(1-piperidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenamine obtained in Reference Example 53.

^1H NMR (CDCl_3) δ : 1.42-1.60 (18H, m), 1.97-2.36 (7H, m),
2.80-2.95 (3H, m), 4.06-4.18 (6H, m), 6.58 (1H, s), 7.09
30 (1H, d, $J = 8.4$ Hz), 7.35 (1H, d, $J = 8.1$ Hz), 7.44 (1H, s), 7.50 (1H, s), 7.55 (1H, s), 8.16 (1H, s).

Example 60

4-(4-Chlorophenyl)-2-phenyl-N-[6-(1-piperidinylmethyl)-
5,6,7,8-tetrahydro-2-naphthalenyl]-1,3-oxazole-5-
5 carboxamide

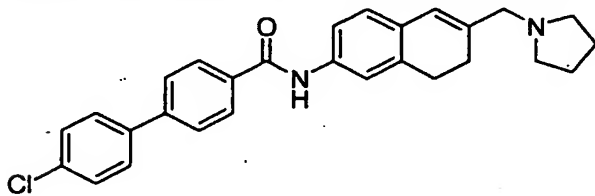


The titled compound was obtained by carrying out the
same operation as in Example 1, using 6-(1-
piperidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenamine
10 obtained in Reference Example 53.

¹H NMR (CDCl₃) δ: 1.26-1.58 (7H, m), 1.90-2.00 (2H, m),
2.22-2.35 (7H, m), 2.70-2.95 (3H, m), 7.06 (1H, d, J = 8.1
Hz), 7.25-7.51 (7H, m), 8.04-8.32 (5H, m).

15 Example 61

4'-Chloro-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-
naphthalenyl][1,1-biphenyl]-4-carboxamide



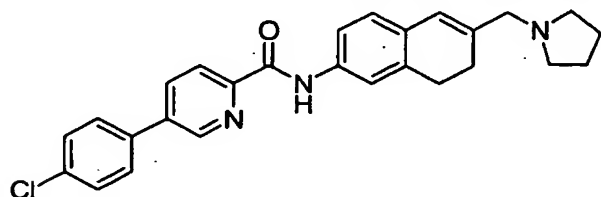
The titled compound was obtained by carrying out the
20 same operation as in Example 51, using 4'-chloro-N-[6-
(chloromethyl)-7,8-dihydro-2-naphthalenyl][1,1'-
biphenyl]-4-carboxamide obtained in Reference Example 56.
Melting point: 185 - 187°C (crystallization solvent:
tetrahydrofuran - n-hexane)

25 ¹H NMR (CDCl₃) δ: 1.83 (4H, s), 2.35 (2H, t, J = 8.1 Hz),
2.52 (4H, s), 2.84 (2H, t, J = 8.1 Hz), 3.18 (2H, s), 6.36
(1H, s), 7.02 (1H, d, J = 8.4 Hz), 7.39-7.56 (6H, m), 7.66

(2H, d, $J = 7.5$ Hz), 7.82 (1H, s), 7.93 (2H, d, $J = 7.5$ Hz).

Example 62

5-(4-Chlorophenyl)-N-[6-(1-pyrrolidinymethyl)-7,8-dihydro-2-naphthalenyl]-2-pyridinecarboxamide

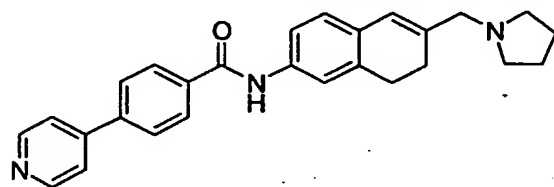


The titled compound was obtained by carrying out the same operation as in Example 51, using 4'-chloro-N-[6-(chloromethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide obtained in Reference Example 56.

^1H NMR (CDCl_3) δ : 1.80 (6H, s), 2.37 (2H, t, $J = 8.1$ Hz), 2.52 (4H, s), 2.87 (2H, t, $J = 8.1$ Hz), 3.18 (2H, s), 6.37 (1H, s), 7.03 (1H, d, $J = 7.8$ Hz), 7.48-7.61 (6H, m), 8.04 (1H, dd, $J = 8.1, 2.1$ Hz), 8.35 (1H, d, $J = 8.1$ Hz), 8.78 (1H, s), 9.95 (1H, s).

Example 63

4-(4-Pyridinyl)-N-[6-(1-pyrrolidinymethyl)-7,8-dihydro-2-naphthalenyl]benzamide

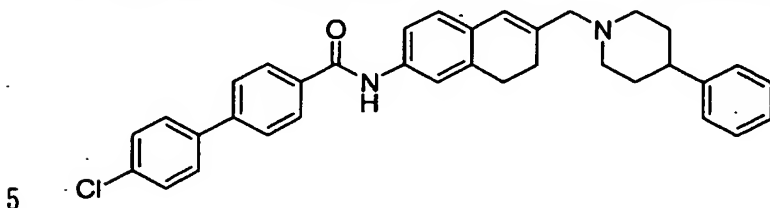


The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(1-pyrrolidinymethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

^1H NMR (CDCl_3) δ : 1.79-1.83 (6H, m), 2.35 (2H, t, $J = 8.1$ Hz), 2.53 (4H, s), 2.73 (2H, t, $J = 8.1$ Hz), 3.18 (2H, s), 6.36 (1H, s), 7.02 (1H, d, $J = 7.8$ Hz), 7.38 (1H, d, $J = 8.1$ Hz), 7.48 (1H, s), 7.71-7.78 (4H, m), 7.89 (1H, s), 7.99 (1H, d, $J = 8.4$ Hz), 8.32 (2H, d, $J = 8.4$ Hz).

Example 64

4'-Chloro-N-[6-[(4-phenyl-1-piperidiny)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



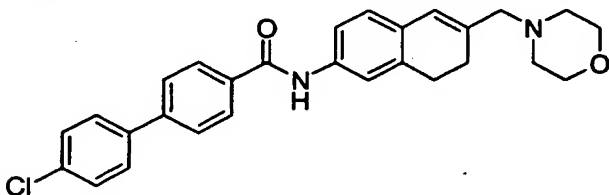
The titled compound was obtained by carrying out the same operation as in Example 51, using 4'-chloro-N-[6-(chloromethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide obtained in Reference Example 56.

10 ^1H NMR (CDCl_3) δ : 1.83-2.10 (6H, m), 2.37 (2H, t, J = 8.1 Hz), 2.47-2.54 (1H, m), 2.86 (2H, t, J = 8.1 Hz), 3.03-3.10 (2H, m), 3.10 (2H, s), 6.37 (1H, s), 7.03 (1H, d, J = 8.4 Hz), 7.19-7.57 (11H, m), 7.66 (2H, d, J = 8.4 Hz), 7.81 (1H, s), 7.94 (2H, d, J = 8.4 Hz).

15 Melting point: 228 - 230°C (crystallization solvent: tetrahydrofuran - n-hexane)

Example 65

20 4'-Chloro-N-[6-(4-morpholinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



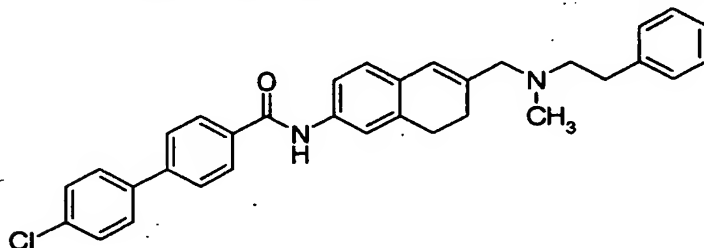
The titled compound was obtained by carrying out the same operation as in Example 51, using 4'-chloro-N-[6-(chloromethyl)-7,8-dihydro-2-naphthalenyl][1,1'-

25 biphenyl]-4-carboxamide obtained in Reference Example 56. ^1H NMR (CDCl_3) δ : 2.34 (2H, t, J = 7.8 Hz), 2.45 (4H, s), 2.84 (2H, t, J = 7.8 Hz), 3.06 (2H, s), 3.73 (4H, s), 6.36 (1H, s), 7.02 (1H, d, J = 8.1 Hz), 7.36-7.57 (6H, m), 7.67 (2H, d, J = 8.4 Hz), 7.80 (1H, s), 7.94 (2H, d, J = 8.4 Hz).

Melting point: 194 - 195°C (crystallization solvent:
tetrahydrofuran - n-hexane)

Example 66

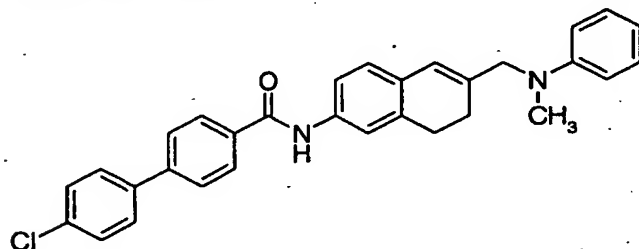
- 5 4'-Chloro-N-(6-[[methyl(2-phenylethyl)amino]methyl]-
7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



- The titled compound was obtained by carrying out the
same operation as in Example 51, using 4'-chloro-N-[6-
10 (chloromethyl)-7,8-dihydro-2-naphthalenyl][1,1'-
biphenyl]-4-carboxamide obtained in Reference Example 56.
¹H NMR (CDCl₃) δ: 2.25-2.32 (2H, m), 2.32 (3H, s), 2.60-2.66
(2H, m), 2.77-2.83 (4H, m), 3.10 (2H, s), 6.32 (1H, s),
6.93-7.95 (16H, m).
15 Melting point: 173 - 175°C (crystallization solvent:
tetrahydrofuran - n-hexane)

Example 67

- 20 4'-Chloro-N-[6-[methylanilino)methyl]-7,8-dihydro-2-
naphthalenyl][1,1'-biphenyl]-4-carboxamide

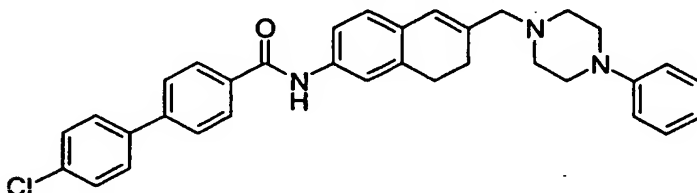


- The titled compound was obtained by carrying out the
same operation as in Example 51, using 4'-chloro-N-[6-
(chloromethyl)-7,8-dihydro-2-naphthalenyl][1,1'-
25 biphenyl]-4-carboxamide obtained in Reference Example 56.
¹H NMR (CDCl₃) δ: 2.20-2.30 (2H, m), 2.25 (3H, s), 2.85-2.90

(2H, m), 3.00 (2H, s), 6.30 (1H, s), 6.74-7.95 (146H, m).
 Melting point: 177 - 179°C (crystallization solvent:
 tetrahydrofuran - n-hexane)

5 Example 68

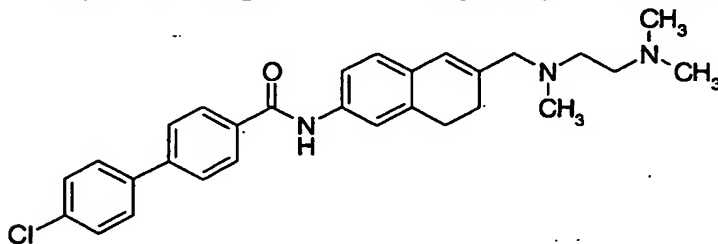
4'-Chloro-N-[6-[(4-phenyl-1-piperadiny)methyl]-7,8-
 dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the
 10 same operation as in Example 51, using 4'-chloro-N-[6-
 (chloromethyl)-7,8-dihydro-2-naphthalenyl][1,1'-
 biphenyl]-4-carboxamide obtained in Reference Example 56.
¹H NMR (CDCl₃) δ: 2.37 (2H, t, J = 8.1 Hz), 2.62 (4h, S),
 2.86 (2H, t, J = 8.4 Hz), 3.13 (2H, s), 3.22 (4H, s), 6.39
 15 (1H, s), 6.85-7.95 (16H, m).
 Melting point: 228 - 230°C (crystallization solvent:
 tetrahydrofuran - n-hexane)

Example 69

20 4'-Chloro-N-[6-[[[2-
 (dimethylamino)ethyl](methyl)amino]methyl]-7,8-dihydro-
 2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



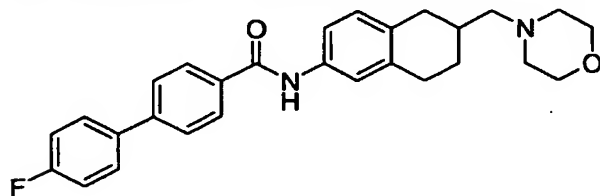
The titled compound was obtained by carrying out the
 25 same operation as in Example 51, using 4'-chloro-N-[6-
 (chloromethyl)-7,8-dihydro-2-naphthalenyl][1,1'-
 biphenyl]-4-carboxamide obtained in Reference Example 56.
¹H NMR (CDCl₃) δ: 2.25 (6H, s), 2.26 (3H, s), 2.33 (2H, t,

J = 8.1 Hz), 2.44-2.50 (4H, m), 2.84 (2H, t, J = 8.1 Hz), 3.07 (2H, s), 6.35 (1H, s), 7.02- (1H, d, J = 8.4 Hz), 7.37-7.57 (6H, m), 7.67 (2H, d, J = 8.1 Hz), 7.80 (1H, s), 7.94 (2H, d, J = 8.4 Hz).

- 5 Melting point: 156 - 158°C (crystallization solvent: tetrahydrofuran - n-hexane)

Example 70

- 4'-Fluoro-N-[6-(4-morpholinylmethyl)-5,6,7,8-
10 tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



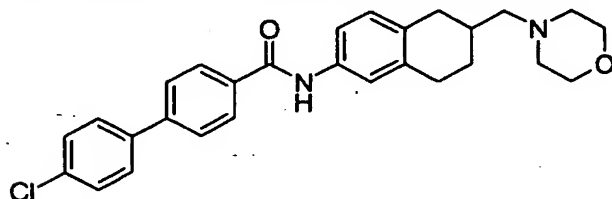
- The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(4-morpholinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenamine
15 obtained in Reference Example 57.

¹H NMR (CDCl₃) δ: 1.40-1.50 (1H, m), 1.90-2.10 (2H, m), 2.29-2.45 (7H, m), 2.80-2.92 (3H, m), 3.72-3.75 (4H, m), 7.07-7.33 (4H, m), 7.46 (1H, s), 7.56-7.66 (4H, m), 7.78 (1H, s), 7.92 (2H, d, J = 8.1 Hz).

- 20 Melting point: 188 - 190°C (crystallization solvent: ethyl acetate)

Example 71

- 4'-Chloro-N-[6-(4-morpholinylmethyl)-5,6,7,8-
25 tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(4-morpholinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenamine

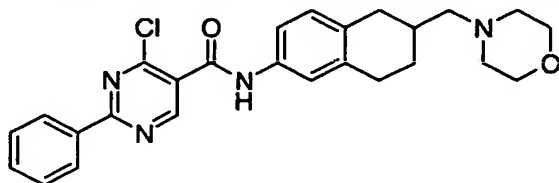
obtained in Reference Example 57.

^1H NMR (CDCl_3) δ : 1.40-1.50 (1H, m), 1.90-2.10 (2H, m), 2.32-2.45 (7H, m), 2.80-2.90 (3H, m), 3.70-3.80 (4H, m), 7.10-7.92 (12H, m).

5 Melting point: 216 - 218°C (crystallization solvent: ethyl acetate)

Example 72

10 4-Chloro-N-[6-(4-morpholinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenyl]-2-phenyl-5-pyrimidinecarboxamide

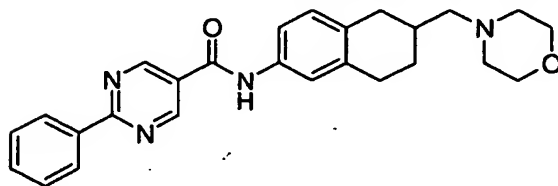


The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(4-morpholinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenamine obtained in Reference Example 57.

15 ^1H NMR (CDCl_3) δ : 1.40-1.50 (1H, m), 1.95-2.05 (2H, m), 2.29-2.45 (7H, m), 2.80-2.95 (3H, m), 3.73 (4H, t, $J = 4.5$ Hz), 7.10 (1H, d, $J = 8.1$ Hz), 7.32 (1H, d, $J = 8.1$ Hz), 7.42 (1H, s), 7.49-7.56 (3H, m), 8.25 (1H, s), 8.48 (2H, d, $J = 6.6$ Hz), 9.20 (1H, s)

Example 73

N-[6-(4-Morpholinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenyl]-2-phenyl-5-pyrimidinecarboxamide



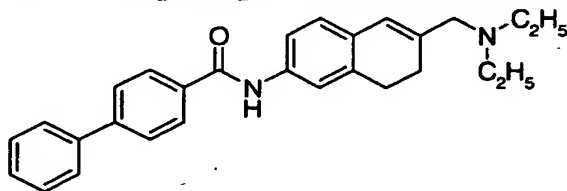
25 The titled compound was obtained by carrying out the same operation as in Reference Example 48, using 4-chloro-N-[6-(4-morpholinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenyl]-2-phenyl-5-pyrimidinecarboxamide obtained in

Example 72.

¹H NMR (CDCl₃) δ: 1.21-1.30 (1H, m), 1.93-2.03 (2H, m), 2.28-2.44 (7H, m), 2.80-2.90 (3H, m), 3.73 (4H, t, J = 4.8 Hz), 7.07 (1H, d, J = 8.1 Hz), 7.26-7.30 (1H, m), 7.39 (1H, s), 7.51-7.53 (3H, m), 8.00 (1H, s), 8.50 (2H, dd, J = 8.1, 2.4 Hz), 9.21 (2H, s)

Example 74

N-[6-[(Diethylamino)methyl]-7,8-dihydro-2-naphthalenyl]
[1,1'-biphenyl]-4-carboxamide



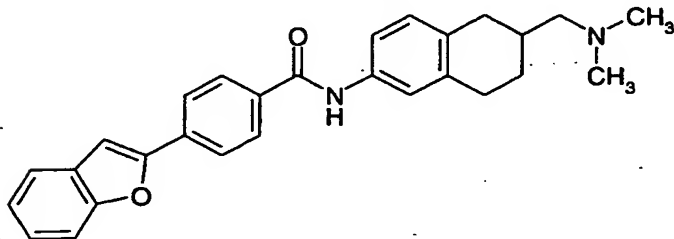
The titled compound was obtained by carrying out the same operation as in Example 51, using N-[6-(chloromethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide obtained in Reference Example 58.

¹H NMR (CDCl₃) δ: 1.24 (6H, t, J = 7.2 Hz), 2.33 (2H, t, J = 5.1 Hz), 2.53 (4H, q, J = 7.2 Hz), 2.84 (2H, t, J = 5.1 Hz), 3.11 (2H, s), 6.36 (1H, s), 7.02 (1H, d, J = 8.1 Hz), 7.37-7.50 (5H, m), 7.63 (2H, d, J = 8.7 Hz), 7.71 (2H, d, J = 8.4 Hz), 7.79 (1H, s), 7.93 (2H, d, J = 8.4 Hz).

Melting point: 153 - 155°C (crystallization solvent: tetrahydrofuran - n-hexane)

Example 75

4-(2-Benzo[b]furanyl)-N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]benzamide



The titled compound was obtained by carrying out the

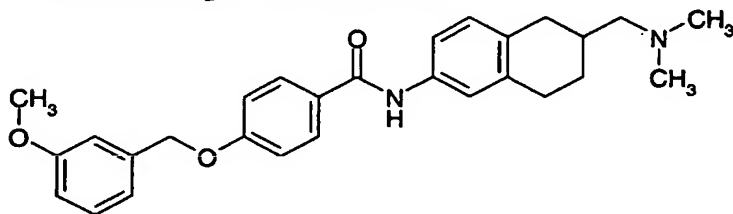
same operation as in Example 4, using 6-amino-2-[(N,N-dimethylamino)methyl]tetralin hydrochloride.

Melting point: 192 - 194°C (crystallization solvent: tetrahydrofuran-isopropyl ether)

5

Example 76

4-(3-Methoxybenzyloxy)-N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]benzamide



10

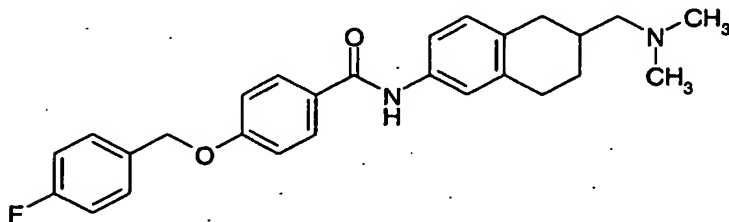
The titled compound was obtained by carrying out the same operation as in Example 4, using 6-amino-2-[(N,N-dimethylamino)methyl]tetralin hydrochloride.

Melting point: 102 - 104°C (crystallization solvent: isopropyl ether)

15

Example 77

4-(4-Fluorobenzyloxy)-N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]benzamide



20

The titled compound was obtained by carrying out the same operation as in Example 4, using 6-amino-2-[(N,N-dimethylamino)methyl]tetralin hydrochloride.

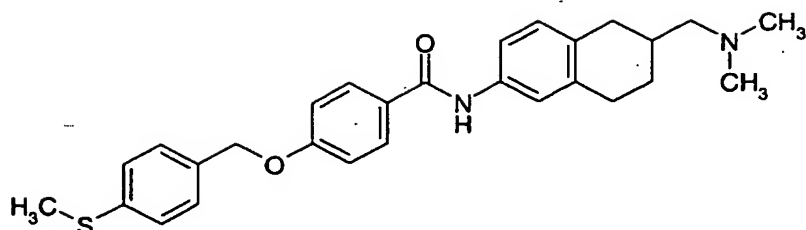
Melting point: 165 - 167°C (crystallization solvent: tetrahydrofuran-hexane)

25

Example 78

4-[4-(Methylsulfanyl)benzyloxy]-N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]benzamide

212.

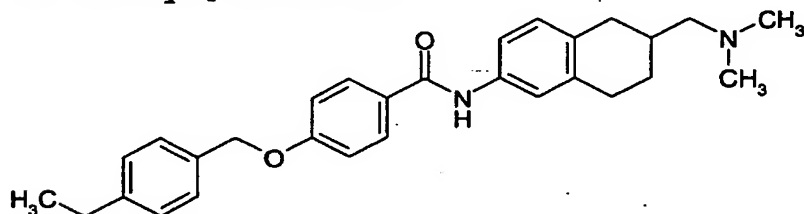


The titled compound was obtained by carrying out the same operation as in Example 4, using 6-amino-2-[(N,N-dimethylamino)methyl]tetralin hydrochloride.

- 5 Melting point: 162 - 163°C (crystallization solvent: tetrahydrofuran-hexane)

Example 79

- 10 4-(4-Ethylbenzyloxy)-N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]benzamide

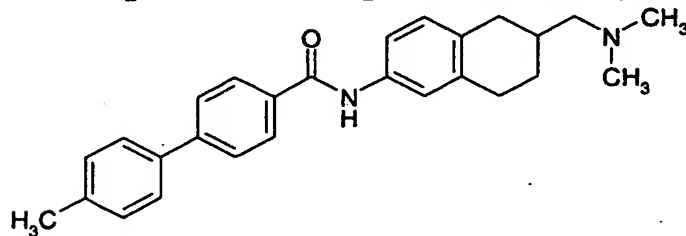


The titled compound was obtained by carrying out the same operation as in Example 4, using 6-amino-2-[(N,N-dimethylamino)methyl]tetralin hydrochloride.

- 15 Melting point: 120 - 122°C (crystallization solvent: tetrahydrofuran-isopropyl ether)

Example 80

- 20 (4'-Methylbiphenyl-4-yl)-N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]carboxamide



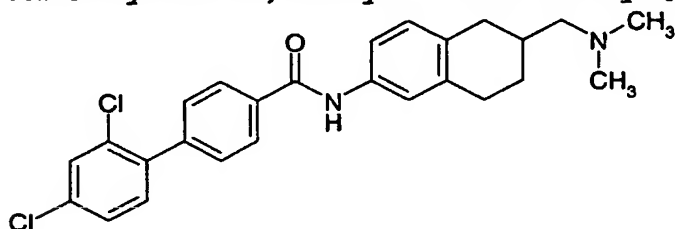
The titled compound was obtained by carrying out the same operation as in Example 4, using 6-amino-2-[(N,N-

dimethylamino)methyl]tetralin hydrochloride.

Melting point: 181 - 182°C (crystallization solvent: ethyl acetate-hexane)

5 Example 81

(2',4'-Dichlorobiphenyl-4-yl)-N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]carboxamide

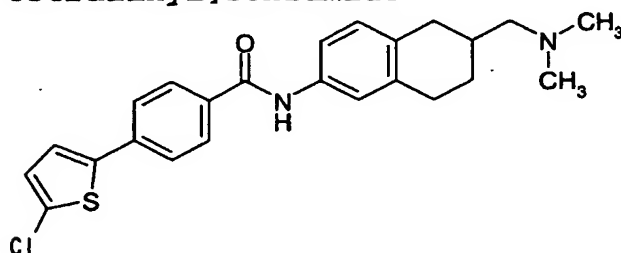


10 The titled compound was obtained by carrying out the same operation as in Example 4, using 6-amino-2-[(N,N-dimethylamino)methyl]tetralin hydrochloride.

Melting point: 188 - 189°C (crystallization solvent: tetrahydrofuran-hexane)

15 Example 82

4-(5-Chloro-2-thienyl-N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]benzamide

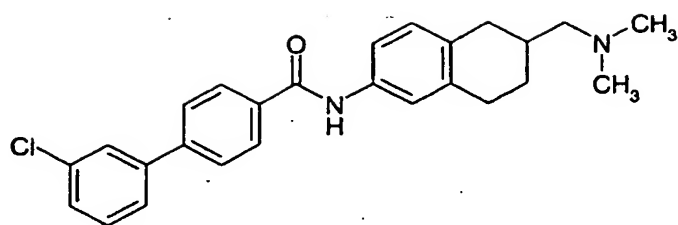


20 The titled compound was obtained by carrying out the same operation as in Example 4, using 6-amino-2-(N,N-dimethylamino)methyltetraline hydrochloride.

Melting point: 167 - 169°C (crystallization solvent: ethyl acetate-hexane)

25 Example 83

(3'-Chlorobiphenyl-4-yl)-N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]carboxamide

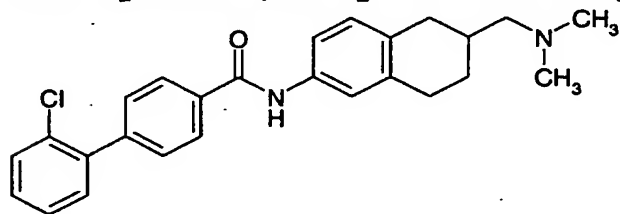


The titled compound was obtained by carrying out the same operation as in Example 4, using 6-amino-2-[(N,N-dimethylamino)methyl]tetralin hydrochloride.

- 5 Melting point: 138 - 139°C (crystallization solvent: tetrahydrofuran-isopropyl ether)

Example 84

- 10 (2'-Chlorobiphenyl-4-yl)-N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]carboxamide

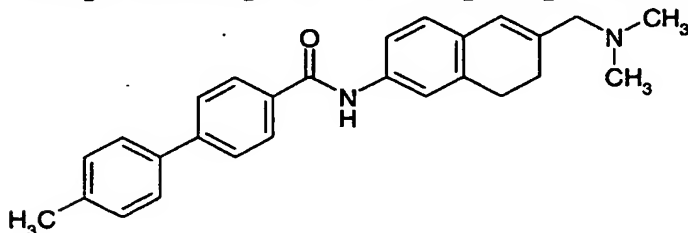


The titled compound was obtained by carrying out the same operation as in Example 4, using 6-amino-2-[(N,N-dimethylamino)methyl]tetralin hydrochloride.

- 15 Melting point: 176 - 177°C (crystallization solvent: tetrahydrofuran-hexane)

Example 85

- 20 4'-Methyl-N-[6-[N,N-dimethylamino)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-[(N,N-dimethylamino)methyl]-7,8-dihydro-2-naphthalenamine

obtained in Example 41-2).

¹H-NMR (CDCl₃) δ: 2.25 (6H, s), 2.33 (2H, t, J = 8.1 Hz),
2.41 (3H, s), 2.84 (2H, t, J = 8.1 Hz), 2.98 (2H, s), 6.33
(1H, s), 7.01 (1H, d, J = 7.8 Hz), 7.39 (1H, d, J = 8.4 Hz),
5 7.48 (1H, s), 7.52 (2H, d, J = 7.8 Hz), 7.67 (2H, d, J =
8.1 Hz), 7.84 (1H, s), 7.91 (2H, d, J = 8.1 Hz).

Elemental analysis for C₂₇H₂₈N₂O

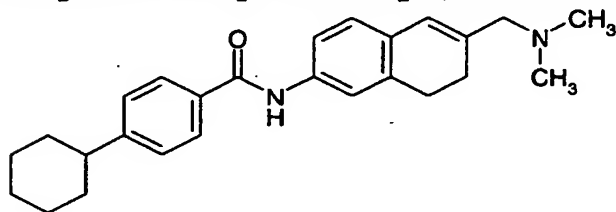
Calcd.: C, 81.78; H, 7.12; N, 7.06

Found: C, 81.51; H, 7.22; N, 6.93

10 Melting point: 195 - 196°C (crystallization solvent: ethyl
acetate-diisopropyl ether)

Example 86

4-Cyclohexyl-N-[6-[(N,N-dimethylamino)methyl]-7,8-
15 dihydro-2-naphthalenyl]benzamide



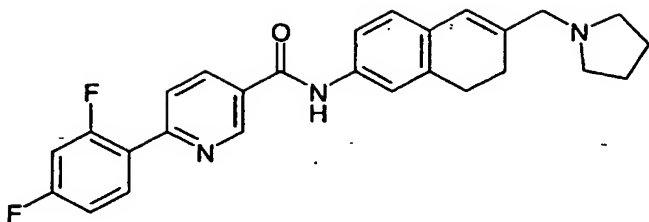
The titled compound was obtained by carrying out the
same operation as in Example 1, using the 6-[(N,N-
dimethylamino)methyl]-7,8-dihydro-2-naphthalenamine
20 obtained in Example 41-2).

¹H-NMR (CDCl₃) δ: 1.20-1.52 (4H, m), 1.71-1.96 (6H, m), 2.25
(6H, s), 2.33 (2H, t, J = 8.1 Hz), 2.50-2.62 (1H, m), 2.84
(2H, t, J = 8.1 Hz), 2.99 (2H, s), 6.33 (1H, s), 7.00 (1H,
d, J = 7.8 Hz), 7.31 (2H, d, J = 8.1 Hz), 7.36 (1H, d, J
25 = 7.8 Hz), 7.46 (1H, brs), 7.75 (1H, s), 7.78 (2H, d, J
= 8.1 Hz).

Melting point: 179 - 181°C (crystallization solvent: ethyl
acetate-diisopropyl ether)

30 Example 87

6-(2,4-Difluorophenyl)-N-[6-[(1-pyrrolidinyl)methyl]-
7,8-dihydro-2-naphthalenyl]nicotinamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.81 (4H, m), 2.37 (2H, t, $J = 8.1$ Hz), 2.54 (4H, m), 2.86 (2H, t, $J = 8.1$ Hz), 3.18 (2H, s), 6.37 (1H, s), 6.93 (1H, m), 7.04 (2H, m), 7.38 (1H, m), 7.47 (1H, s), 7.77 (1H, s), 7.91 (1H, m), 8.13 (1H, m), 8.24 (1H, m), 9.16 (1H, s).

Elemental analysis for $\text{C}_{27}\text{H}_{26}\text{F}_2\text{N}_3\text{O}$

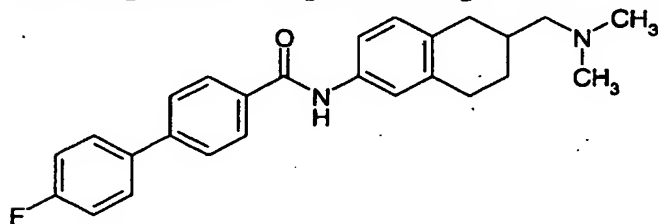
Calcd.: C, 72.79; H, 5.66; N, 9.43

Found: C, 72.65; H, 5.52; N, 9.73

Melting point: 169 - 170°C (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 88

4'-Fluoro-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 4, using 6-amino-2-[(N,N-dimethylamino)methyl]tetralin hydrochloride.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.41 (1H, m), 1.95 (2H, m), 2.25-2.45 (3H, m), 2.36 (6H, s), 2.85-2.94 (3H, m), 7.13 (3H, m), 7.30 (1H, m), 7.46 (1H, s), 7.59 (2H, m), 7.65 (2H, d, $J = 8.1$ Hz), 7.74 (1H, s), 7.93 (2H, d, $J = 8.1$ Hz).

Elemental analysis for $\text{C}_{26}\text{H}_{27}\text{FN}_2\text{O}$

Calcd.: C, 77.58; H, 6.76; N, 6.96

Found: C, 77.72; H, 6.49; N, 6.79

Melting point: 184 - 186°C (crystallization solvent: ethyl acetate - diisopropyl ether)

5

Example 89

(+)-4'-Fluoro-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide, and (-)-4'-fluoro-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide

Optical resolution of 4'-fluoro-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide (2.00 g) obtained in Example 88 was conducted by sample-splitting HPLC using a chiral column (Daicel Co., CHIRALCEL OD 500 mmD x 500 mmL; moving phase n-hexane:ethanol = 85:15), to give (+) form (1.00 g; 99.8%ee) and (-) form (0.89 g; >99.9%ee) as powders. The powders obtained were respectively recrystallized using ethyl acetate - diisopropyl ether, to give the (+) form (855 mg) and (-) form (754 mg) of the titled compounds. The optical rotation of both compounds are shown below.

(+)-4'-fluoro-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide

Optical rotation: $[\alpha]_D = +50.8^\circ$ C=0.494% (methanol)

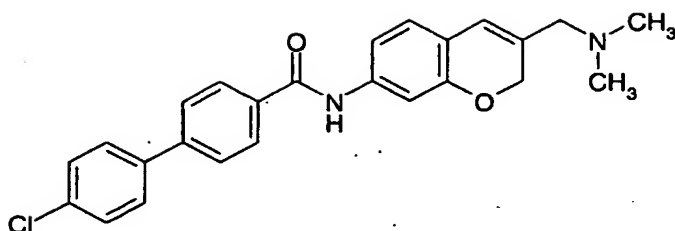
(-)-4'-fluoro-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide

Optical rotation: $[\alpha]_D = +51.2^\circ$ C=0.492% (methanol)

30

Example 90

4'-Chloro-N-[3-[(N,N-dimethylamino)methyl]-2H-chromen-7-yl][1,1'-biphenyl]-4-carboxamide



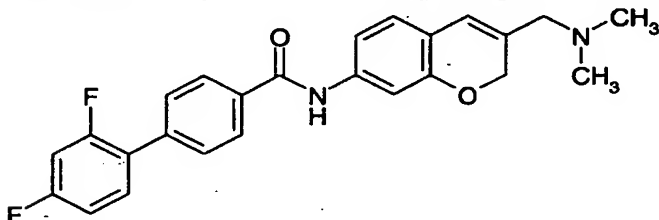
The titled compound was obtained by carrying out the same operation as in Example 1, using 3-[(N,N-dimethylamino)methyl]-2H-chromen-7-amine obtained in Reference Example 59.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.23 (6H, s), 2.97 (2H, s), 4.79 (2H, s), 6.30 (1H, s), 6.96 (1H, d, $J = 8.1$ Hz), 7.13 (1H, s), 7.20 (1H, d, $J = 8.1$ Hz), 7.45 (2H, d, $J = 8.6$ Hz), 7.56 (2H, d, $J = 8.6$ Hz), 7.66 (2H, d, $J = 8.4$ Hz), 7.74 (1H, brs), 7.93 (2H, d, $J = 8.4$ Hz).

Melting point: 199 - 208°C (crystallization solvent: diisopropyl ether)

Example 91

2',4'-Difluoro-N-[3-[(N,N-dimethylamino)methyl]-2H-chromen-7-yl][1,1'-biphenyl]-4-carboxamide



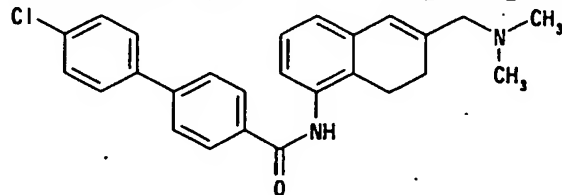
The titled compound was obtained by carrying out the same operation as in Example 1, using 3-[(N,N-dimethylamino)methyl]-2H-chromen-7-amine obtained in Reference Example 59.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.23 (6H, s), 2.97 (2H, s), 4.78 (2H, s), 6.29 (1H, s), 6.80-7.10 (2H, m), 6.96 (1H, d, $J = 8.1$ Hz), 7.13 (1H, s), 7.20 (1H, d, $J = 8.1$ Hz), 7.40-7.50 (1H, m), 7.62 (2H, d, $J = 8.4$ Hz), 7.76 (1H, brs), 7.92 (2H, d, $J = 8.4$ Hz).

Melting point: 200 - 204°C (crystallization solvent: diisopropyl ether)

Example 92

4'-Chloro-N-[6-[(dimethylamino)methyl]-7,8-dihydro-1-naphthalenyl][1,1'-biphenyl]-4-carboxamide



5

The titled compound was obtained in the same manner as in Example 1, using 6-[(dimethylamino)methyl]-7,8-dihydro-1-naphthalenamine obtained in Reference Example 60.

10

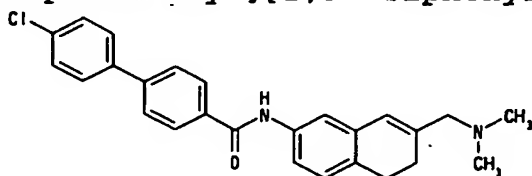
¹H-NMR (CDCl₃) δ: 2.34 (6H, s), 2.36 (2H, t, J=8.1 Hz), 2.80 (2H, t, J=8.1 Hz), 3.00 (2H, s), 6.38 (1H, s), 6.94 (1H, d, J=7.8 Hz), 7.21 (1H, t, J=7.8 Hz), 7.45 (2H, d, J=8.6 Hz), 7.56 (2H, d, J=8.6 Hz), 7.61 (2H, m), 7.68 (2H, d, J=8.4 Hz), 7.97 (2H, d, J=8.4 Hz).

15

Melting point: 193 - 195°C (crystallization solvent : diisopropyl ether)

Example 93

20 4'-Chloro-N-[7-[(dimethylamino)methyl]-5,6-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



25

The titled compound was obtained as a white powder by the same method as in Example 1, using 7-[(dimethylamino)methyl]-5,6-dihydro-2-naphthalenamine obtained in Reference Example 61.

¹H-NMR (CDCl₃) δ: 2.25 (6H, s), 2.34 (2H, t, J=8.1 Hz), 2.82 (2H, t, J=8.1 Hz), 3.00 (2H, s), 6.36 (1H, s), 7.11 (1H, d, J=7.5 Hz), 7.34 (1H, d, J=8.1 Hz), 7.38 (1H, s), 7.44

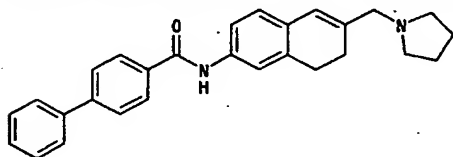
(2H, d, J=8.4 Hz), 7.56 (2H, d, J=8.4 Hz), 7.66 (2H, d, J=8.4 Hz), 7.78 (1H, brs), 7.97 (2H, d, J=8.4 Hz).

Melting point: 167 - 169°C (crystallization solvent : diisopropyl ether)

5

Example 94

N-[6-(1-Pyrrolidinymethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



10 The titled compound was obtained as a white powder in the same manner as in Example 1, using 6-(1-pyrrolidinymethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

¹H-NMR (CDCl₃) δ : 1.75-1.90 (4H, m), 2.34 (2H, t, J=8.1 Hz),
15 2.45-2.60 (4H, m), 2.85 (2H, t, J=8.1 Hz), 3.18 (2H, s), 6.36 (1H, s), 7.02 (1H, d, J=8.1 Hz), 7.27-7.55 (5H, m), 7.63 (2H, d, J=7.3 Hz), 7.70 (2H, d, J=8.4 Hz), 7.82 (1H, s), 7.94 (2H, d, J=8.1 Hz).

Elemental analysis for C₂₈H₂₈N₂O

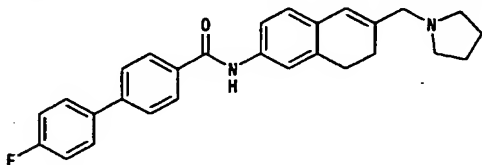
20 Calcd.: C, 82.32; H, 6.91; N, 6.86.

Found: C, 81.99; H, 6.69; N, 6.91.

Melting point: 176 - 177°C (crystallization solvent : diisopropyl ether)

25 Example 95

4'-Fluoro-N-[6-(1-pyrrolidinymethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



30 The titled compound was obtained in the same manner as in Example 1, using 6-(1-pyrrolidinymethyl)-7,8-

dihydro-2-naphthalenamine obtained in Reference Example 54..

¹H-NMR (CDCl₃) δ : 1.75-1.90 (4H, m), 2.35 (2H, t, J=8.2 Hz),
2.45-2.60 (4H, m), 2.84 (2H, t, J=8.2 Hz), 3.18 (2H, s),
5 6.36 (1H, s), 7.01 (1H, d, J=8.1 Hz), 7.16 (2H, t, J=8.1 Hz),
7.38 (1H, d, J=8.1 Hz), 7.48 (1H, brs), 7.56-7.61 (2H, m),
7.64 (2H, d, J=8.4 Hz), 7.83 (1H, s), 7.93 (2H, d, J=8.4 Hz).

Elemental analysis for C₂₈H₂₇N₂O

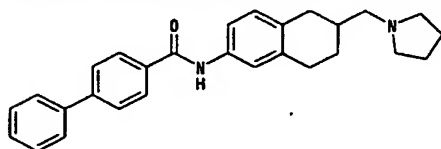
10 Calcd.: C, 78.85; H, 6.38; N, 6.57.

Found: C, 78.75; H, 6.39; N, 6.45.

Melting point: 189 - 192°C (crystallization solvent :
diisopropyl ether)

15 Example 96

N-[6-(1-Pyrrolidinymethyl)-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



20 The titled compound was obtained as a white powder in the same manner as in Example 1, using 6-(1-pyrrolidinymethyl)-5,6,7,8-tetrahydro-2-naphthalenamine obtained in Reference Example 55.

¹H-NMR (CDCl₃) δ : 1.40-1.50 (1H, m), 1.80 (4H, m), 1.80-2.10 (1H, m), 1.80-2.20 (8H, m), 3.30-4.00 (3H, m), 7.29 (1H, d, J=8.4 Hz),
25 7.25-7.30 (1H, m), 7.30-7.55 (4H, m), 6.43 (2H, d, J=7.0 Hz), 7.70 (2H, t, J=8.4 Hz), 7.75 (1H, s), 7.94 (2H, d, J=8.4 Hz).

Elemental analysis for C₂₈H₃₀N₂O

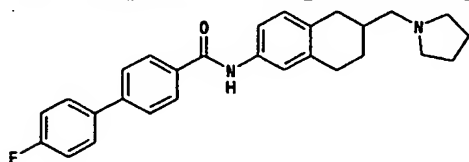
Calcd.: C, 81.91; H, 7.37; N, 6.82.

30 Found: C, 81.53; H, 7.25; N, 6.86.

Melting point: 144 - 146°C (crystallization solvent :
diisopropyl ether)

Example 97

4'-Fluoro-N-[6-(1-pyrrolidinymethyl)-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



5 The titled compound was obtained as a white powder in the same manner as in Example 1, using 6-(1-pyrrolidinymethyl)-5,6,7,8-tetrahydro-2-naphthalenamine obtained in Reference Example 55.

¹H-NMR (CDCl₃) δ: 1.40-1.50 (1H, m), 1.80 (4H, m), 1.80-2.10 (1H, m), 1.80-2.20 (8H, m), 3.30-4.00 (3H, m), 7.08 (1H, d, J=8.1 Hz), 7.15 (2H, t, J=8.4 Hz), 7.30 (1H, d, J=8.1 Hz), 7.44 (1H, brs), 7.56-7.61 (2H, m), 7.62 (2H, d, J=8.1 Hz), 7.85 (1H, s), 7.92 (2H, d, J=8.1 Hz).

Elemental analysis for C₂₈H₂₉FN₂O

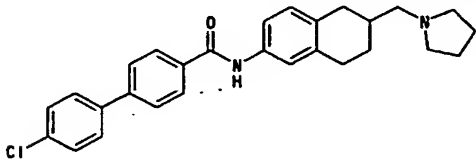
15 Calcd.: C, 78.48; H, 6.82; N, 6.54.

Found: C, 78.18; H, 6.60; N, 6.60.

Melting point: 185 - 189°C (crystallization solvent : diisopropyl ether)

20 Example 98

4'-Chloro-N-[6-(1-pyrrolidinymethyl)-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



25 The titled compound was obtained as a white powder in the same manner as in Example 1, using 6-(1-pyrrolidinymethyl)-5,6,7,8-tetrahydro-2-naphthalenamine obtained in Reference Example 55.

¹H-NMR (CDCl₃) δ: 1.40-1.50 (1H, m), 1.80 (4H, m), 1.80-2.10 (1H, m), 1.80-2.20 (8H, m), 3.30-4.00 (3H, m), 7.08 (1H, d, J=8.1 Hz), 7.31 (1H, d, J=8.4 Hz), 7.43 (2H, d, J=8.7 Hz), 7.45 (1H, s), 7.54 (2H, d, J=8.7 Hz), 7.64 (2H, d, J=8.4

Hz), 7.80 (1H, s), 7.93 (2H, d, J=8.4 Hz).

Elemental analysis for $C_{28}H_{29}ClN_2O$

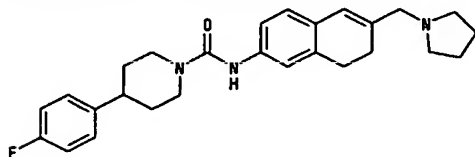
Calcd.: C, 75.57; H, 6.57; N, 6.30.

Found: C, 75.26; H, 6.68; N, 6.15.

- 5 Melting point: 206 - 209°C (crystallization solvent : diisopropyl ether)

Example 99

- 10 4-(4-Fluorophenyl)-N-[6-(1-piperidinylmethyl)-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide



- 6-(1-Pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54 (50 mg, 0.22 mmol) and pyridine (35 mg, 0.44 mmol) were dissolved in tetrahydrofuran (3 ml). Phenyl chlorocarbonate (38 mg, 0.24 mol) was added to the solution under ice-cooling, which was stirred for 10 minutes. The reaction mixture was concentrated, and dimehtylsulfoxide (5 ml) was added to the residue. 4-(4-Fluorophenyl)piperidine hydrochloride (57 mg, 0.26 mmol) and 4N aqueous sodium hydroxide solution (0.066 ml, 0.26 mmol) were added to the reaction mixture at room temperature while stirring, which was stirred for 30 minutes. Ethyl acetate and water were added to the mixture, and extraction was conducted. The organic layer was washed with water, and concentrated. Diisopropyl ether was added to the residue. The crystallized product was collected by filtration, washed with diisopropyl ether, to give 4-(4-fluorophenyl)-N-[6-(1-piperidinylmethyl)-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide (48 mg) as a white powder.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.60-1.70 (2H, m), 1.79 (4H, m), 1.80-1.90 (2H, m), 2.33 (2H, t, J=7.8 Hz), 2.51 (4H, m), 2.60-2.70 (1H, m), 2.80 (2H, t, J=7.8 Hz), 2.90-3.10 (2H, m), 3.16

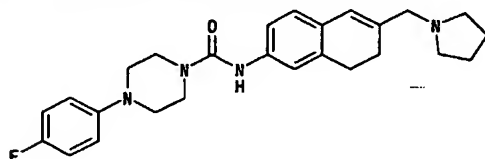
(2H, s), 4.18-4.23 (2H, m), 6.32 (1H, s), 6.32 (1H, s), 6.92-7.09 (4H, m), 7.15-7.20 (3H, m).

Melting point: 182 - 185°C (crystallization solvent : diisopropyl ether)

5

Example 100

4-(4-Fluorophenyl)-N-[6-(1-pyrrolidinymethyl)-7,8-dihydro-2-naphthalenyl]-1-piperazinecarboxamide



10 The titled compound was obtained as a white powder in the same manner as in Example 99, using 6-(1-pyrrolidinymethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54 and 4-fluorophenylpiperazine.

15 ¹H-NMR (CDCl₃) δ: 1.79 (4H, m), 2.32 (2H, t, J=7.8 Hz), 2.51 (4H, m), 2.80 (2H, t, J=7.8 Hz), 3.13-3.16 (4H, m), 3.16 (2H, s), 3.63-3.66 (4H, m), 6.30 (1H, s), 6.32 (1H, s), 6.88-7.08 (6H, m), 7.19 (1H, s).

Elemental analysis for C₂₆H₃₁FN₄O

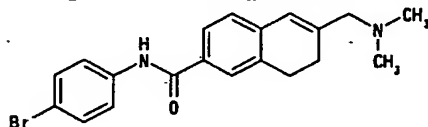
20 Calcd.: C, 71.86; H, 7.19; N, 12.89.

Found: C, 71.68; H, 7.35; N, 12.65.

Melting point: 179 - 181°C (crystallization solvent : diisopropyl ether)

25 Example 101

N-(4-Bromophenyl)-6-[(dimethylamino)methyl]-7,8-dihydro-2-naphthalenecarboxamide



30 1) 6-Cyano-1-tetralone (1.30 g, 7.59 mmol) synthesized by a known method by documents (synthetic communications, 23(21), 2965 (1993)) was dissolved in a

mixed solution of concentrated hydrochloric acid (10 ml) and acetic acid (20 ml), which was stirred at 120°C for 16 hours. The reaction mixture was concentrated. Ethyl acetate and water were added to the residue, and extraction was conducted. The organic layer was washed with water, and concentrated. The residue was washed with ethyl acetate - n-hexane (1:1), to give 5-oxo-5,6,7,8-tetrahydro-2-naphthalenecarboxylic acid (1.10 g) as a white powder.

¹H-NMR (CDCl₃) δ: 2.15-2.23 (2H, m), 2.70-2.75 (2H, m), 3.04-3.07 (2H, m), 8.01-8.03 (1H, m), 8.03 (1H, s), 8.13 (1H, d, J=8.7 Hz).

2) N-(4-Bromophenyl)-5-oxo-5,6,7,8-tetrahydro-2-naphthalenecarboxamide (1.21 g) was obtained as a white powder in the same manner as in Example 1, using 5-oxo-5,6,7,8-tetrahydro-2-naphthalenecarboxylic acid (1.00 g, 5.26 mmol) obtained in 1) and 4-bromoaniline (0.90 g, 5.26 mmol).

¹H-NMR (CDCl₃) δ: 2.14-2.23 (2H, m), 2.69-2.73 (2H, m), 3.03-3.07 (2H, m), 7.48-7.58 (4H, m), 7.71 (1H, d, J=8.1 Hz), 7.79 (1H, s), 7.86 (1H, s), 8.12 (1H, d, J=8.1 Hz).

3) N-(4-Bromophenyl)-5-oxo-5,6,7,8-tetrahydro-2-naphthalenecarboxamide (1.10 g, 3.19 mmol) obtained in 2) was dissolved in dimethylformamide diethylacetal (30 ml), which was refluxed with heating for 4 hours. The crystallized product was collected by filtration, washed with ethyl acetate, to give N-(4-bromophenyl)-6-[(dimethylamino)methylidene]-5-oxo-5,6,7,8-tetrahydro-2-naphthalenecarboxamide (1.21 g) as a yellow powder.

¹H-NMR (CDCl₃) δ: 2.80-2.87 (4H, m), 3.07 (6H, m), 7.46-7.72 (7H, m), 7.91 (1H, d, J=8.4 Hz), 8.53 (1H, s).

4) Sodium triacetoxhydroborate (398 mg, 1.87 mmol) was dissolved in a mixed solution of acetic acid (40 ml) and tetrahydrofuran (10 ml) under ice-cooling. N-(4-Bromophenyl)-6-[(dimethylamino)methylidene]-5-oxo-5,6,7,8-tetrahydro-2-naphthalenecarboxamide (500 mg,

1.25 mmol) obtained in 3) was added to the solution, which was stirred for 1 hour. The reaction mixture was concentrated under reduced pressure at room temperature.

2-Propanol (50 ml) was added to the residue, and sodium borohydride (142 mg, 3.75 mmol) was further added under ice-cooling. After stirring for 2 hours, the reaction mixture was concentrated. Sodium hydrogencarbonate solution and ethyl acetate was added to the residue for liquid separation. The organic layer was concentrated.

The residue was dissolved in a mixed solution of acetic acid (20 ml) and concentrated hydrochloric acid (20 ml), which was stirred at 70°C for 5 hours. The reaction mixture was concentrated. 4N aqueous sodium hydroxide solution and ethyl acetate were added to the residue, and extraction was conducted. The organic layer was washed with water, and concentrated. The residue was purified by alumina column chromatography (development solvent: ethyl acetate), and the eluent was washed with diisopropyl ether, to give the titled compound (234 mg) as a white powder.

¹H-NMR (CDCl₃) δ: 2.26 (6H, s), 2.38 (2H, t, J=8.1 Hz), 2.89 (2H, t, J=8.1 Hz), 3.02 (2H, s), 6.42 (1H, s), 7.10 (1H, d, J=8.6 Hz), 7.47 (2H, d, J=8.9 Hz), 7.55 (2H, d, J=8.9 Hz), 7.61 (1H, s), 7.62 (1H, d, J=6.7 Hz), 7.76 (1H, s).

Elemental analysis for C₂₀H₂₁BrN₂O

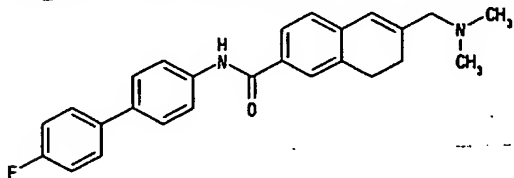
Calcd.: C, 62.35; H, 5.49; N, 7.27.

Found: C, 61.98; H, 5.43; N, 7.07.

Melting point: 175 - 179°C (crystallization solvent : diisopropyl ether)

Example 102

6-[(Dimethylamino)methyl]-N-(4'-fluoro[1,1'-biphenyl]-4-yl)-7,8-dihydro-2-naphthalenecarboxamide



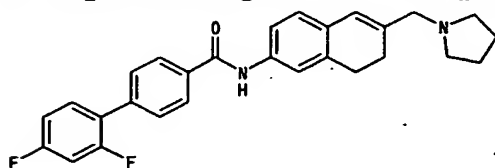
The titled compound was obtained as a white powder, by the same method as in Example 16, using N-(4-bromophenyl)-6-[(dimethylamino)methyl]-7,8-dihydro-2-naphthalenecarboxamide (170 mg, 0.44 mmol) obtained in
5 Example 101 and 4-fluorophenylboric acid (74 mg, 0.53 mmol).

¹H-NMR (CDCl₃) δ: 2.27 (6H, s), 2.39 (2H, t, J=8.4 Hz), 2.91 (2H, t, J=8.4 Hz), 3.02 (2H, s), 6.43 (1H, s), 7.09-7.16 (3H, m), 7.52-7.73 (8H, m), 7.81 (1H, s).

10 Melting point: 200 - 204°C (crystallization solvent : diisopropyl ether)

Example 103

2',4'-Difluoro-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-
15 2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained as a white powder by the same method as in Example 1, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine
20 obtained in Reference Example 54.

¹H-NMR (CDCl₃) δ: 1.75-1.90 (4H, m), 2.36 (2H, t, J=8.1 Hz), 2.45-2.60 (4H, m), 2.85 (2H, t, J=8.1 Hz), 3.18 (2H, s), 6.36 (1H, s), 6.92-7.03 (3H, m), 7.36-7.45 (2H, m), 7.48 (1H, s), 7.62 (2H, d, J=8.4 Hz), 7.78 (1H, s), 7.94 (2H, d, J=8.4 Hz).

25 Elemental analysis for C₂₈H₂₆F₂N₂O

Calcd.: C, 75.66; H, 5.90; N, 6.30.

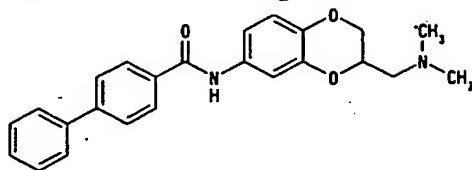
Found: C, 75.36; H, 5.92; N, 6.10.

Melting point: 165 - 167°C (crystallization solvent :
30 diisopropyl ether).

Example 104

N-[3-[(Dimethylamino)methyl]-2,3-dihydro-1,4-

benzodioxin-6-yl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained as a white powder by the same method as in Example 1, using N,N-dimethyl-N-[(7-amino-2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amine obtained in Reference Example 62.

¹H-NMR (CDCl₃) δ: 2.33 (6H, s), 2.48-2.66 (2H, m), 3.93-3.99 (1H, m), 4.27-4.31 (2H, m), 6.86 (1H, d, J=8.6 Hz), 7.03-7.07 (1H, m), 7.31-7.32 (1H, m), 7.37-7.49 (3H, m), 7.62 (2H, d, J=7.0 Hz), 7.68 (2H, d, J=8.4 Hz), 7.76 (1H, s), 7.91 (2H, d, J=8.4 Hz).

Elemental analysis for C₂₄H₂₄N₂O₃

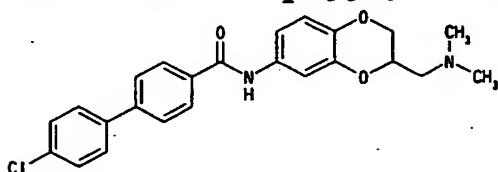
Calcd.: C, 74.21; H, 6.23; N, 7.21.

Found: C, 74.17; H, 6.23; N, 7.01.

Melting point: 124 - 126°C (crystallization solvent : diisopropyl ether)

Example 105

4'-Chloro-N-[3-[(dimethylamino)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl][1,1'-biphenyl]-4-carboxamide



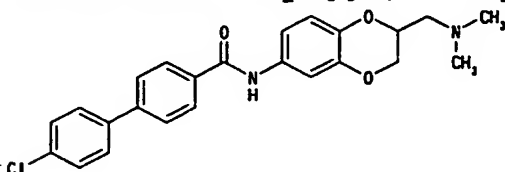
The titled compound was obtained as a white powder by the same method as in Example 1, using N,N-dimethyl-N-[(7-amino-2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amine obtained in Reference Example 62.

¹H-NMR (CDCl₃) δ: 2.33 (6H, s), 2.50-2.67 (2H, m), 3.94-4.01 (1H, m), 4.28-4.31 (2H, m), 6.86 (1H, d, J=8.7 Hz), 7.03-7.06 (1H, m), 7.31 (1H, m), 7.44 (2H, d, J=8.4 Hz), 7.55 (2H, d, J=8.4 Hz), 7.65 (2H, d, J=8.1 Hz), 7.67 (1H, s), 7.91 (2H, d, J=8.1 Hz).

Melting point: 158 - 159°C (crystallization solvent : diisopropyl ether)

Example 106

- 5 4'-Chloro-N-[2-[(dimethylamino)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl][1,1'-biphenyl]-4-carboxamide



- The titled compound was obtained as a white powder by the same method as in Example 1, using N,N-dimethyl-N-
10 [(6-amino-2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amine obtained in Reference Example 63.

- ¹H-NMR (CDCl₃) δ: 2.34 (6H, s), 2.46-2.67 (2H, m), 3.94-4.01 (1H, m), 4.28-4.34 (2H, m), 6.91 (1H, d, J=8.6 Hz),
7.02-7.05 (1H, m), 7.30 (1H, m), 7.44 (2H, d, J=8.4 Hz),
15 7.55 (2H, d, J=8.4 Hz), 7.66 (2H, d, J=8.1 Hz), 7.70 (1H, s), 7.92 (2H, d, J=8.1 Hz).

Elemental analysis for C₂₄H₂₃ClN₂O₃

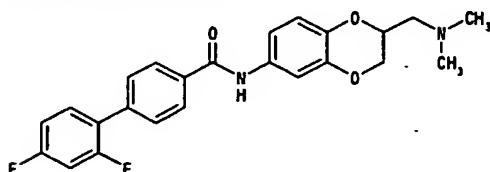
Calcd.: C, 68.16; H, 5.48; N, 6.62.

Found: C, 68.09; H, 5.29; N, 6.57.

- 20 Melting point: 215 - 217°C (crystallization solvent : diisopropyl ether)

Example 107

- 25 2',4'-Difluoro-N-[2-[(dimethylamino)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl][1,1'-biphenyl]-4-carboxamide



- The titled compound was obtained as a white powder by the same method as in Example 1, using N,N-dimethyl-N-
30 [(6-amino-2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amine

obtained in Reference Example 63.

¹H-NMR (CDCl₃) δ: 2.34 (6H, s), 2.50-2.63 (2H, m), 3.94-4.01 (1H, m), 4.28-4.34 (2H, m), 6.91 (1H, d, J=8.6 Hz), 6.91-7.03 (3H, m), 7.30 (1H, m), 7.40-7.50 (1H, m), 7.61 (2H, d, J=8.1 Hz), 7.69 (1H, s), 7.92 (2H, d, J=8.1 Hz).

Elemental analysis for C₂₄H₂₂F₂N₂O₃

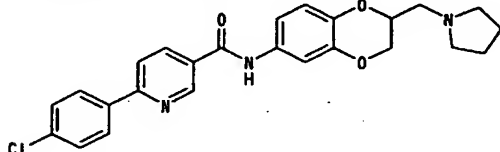
Calcd.: C, 67.91; H, 5.22; N, 6.60.

Found: C, 67.75; H, 5.09; N, 6.48.

Melting point: 209 - 210°C (crystallization solvent : diisopropyl ether)

Example 108

6-(4-Chlorophenyl)-N-[2-(1-pyrrolidinylmethyl)-2,3-dihydro-1,4-benzodioxin-6-yl]nicotinamide



The titled compound was obtained as a white powder by the same method as in Example 1, using 1-[(6-amino-2,3-dihydro-1,4-benzodioxin-2-yl)methyl]pyrrolidine obtained in Reference Example 64.

¹H-NMR (CDCl₃) δ: 1.81 (4H, m), 2.50-2.63 (4H, m), 2.75-2.77 (2H, m), 3.90-4.10 (1H, m), 4.30-4.36 (2H, m), 6.91 (1H, d, J=8.6 Hz), 7.00-7.10 (1H, m), 7.26 (1H, m), 7.48 (2H, d, J=8.6 Hz), 7.72 (1H, s), 7.81 (1H, d, J=7.8 Hz), 8.01 (2H, d, J=8.6 Hz), 8.20-8.25 (1H, m), 9.10 (1H, s).

Elemental analysis for C₂₅H₂₄ClN₃O₃

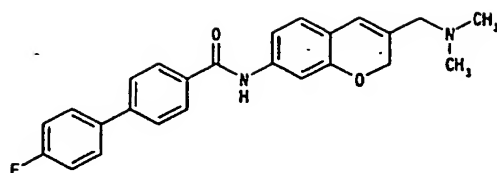
Calcd.: C, 66.74; H, 5.38; N, 9.34.

Found: C, 66.66; H, 5.46; N, 9.11.

Melting point: 218 - 220°C (crystallization solvent : diisopropyl ether)

Example 109

N-[3-[(Dimethylamino)methyl]-2H-chromen-7-yl]-4'-fluoro[1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 3-[(N,N-dimethylamino)methyl]-2H-chromen-7-amine obtained in

5 Reference Example 59.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.23 (6H, s), 2.97 (2H, s), 4.79 (2H, s), 6.30 (1H, s), 6.96 (1H, d, $J=8.1$ Hz), 7.13-7.22 (4H, m), 7.56-7.61 (2H, m), 7.65 (2H, d, $J=8.4$ Hz), 7.78 (1H, s), 7.92 (2H, d, $J=8.4$ Hz).

10 Elemental analysis for $\text{C}_{25}\text{H}_{23}\text{FN}_2\text{O}_2$

Calcd.: C, 74.61; H, 5.76; N, 6.96.

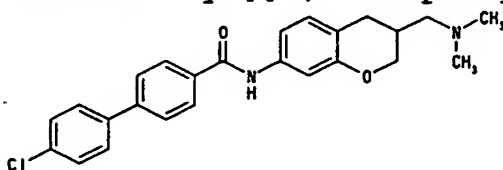
Found: C, 74.35; H, 5.68; N, 6.74.

Melting point: 192 - 195°C (crystallization solvent : diisopropyl ether)

15

Example 110

4'-Chloro-N-[3-[(dimethylamino)methyl]-3,4-dihydro-2H-chromen-7-yl][1,1'-biphenyl]-4-carboxamide



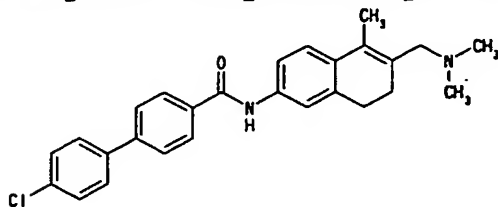
20

The titled compound was obtained by carrying out the same operation as in Example 1, using N-[(7-amino-3,4-dihydro-2H-chromen-3-yl)methyl]-N,N-dimethylamine obtained in Reference Example 65.

25 $^1\text{H-NMR}$ (CDCl_3) δ : 2.26 (6H, s), 2.27 (3H, m), 2.47-2.51 (1H, m), 2.83-2.89 (1H, m), 3.82-3.86 (1H, m), 4.28-4.32 (1H, m), 7.04 (1H, d, $J=8.1$ Hz), 7.12-7.18 (2H, m), 7.44 (2H, d, $J=8.4$ Hz), 7.56 (2H, d, $J=8.4$ Hz), 7.67 (2H, d, $J=8.4$ Hz), 7.71 (1H, s), 7.93 (2H, d, $J=8.4$ Hz).

30 Example 111

4'-Chloro-N-[6-[(dimethylamino)methyl]-5-methyl-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-[(dimethylamino)methyl]-5-methyl-7,8-dihydro-2-naphthalenamine obtained in Reference Example 66.

¹H-NMR (CDCl₃) δ: 2.09 (3H, s), 2.27 (6H, s), 2.31-2.37 (2H, m), 2.74-2.79 (2H, m), 3.08 (2H, s), 7.27-7.30 (1H, m), 7.44-7.48 (4H, m), 7.56 (2H, d, J=8.6 Hz), 7.67 (2H, d, J=8.4 Hz), 7.79 (1H, s), 7.95 (2H, d, J=8.4 Hz).

Elemental analysis for C₂₇H₂₇ClN₂O

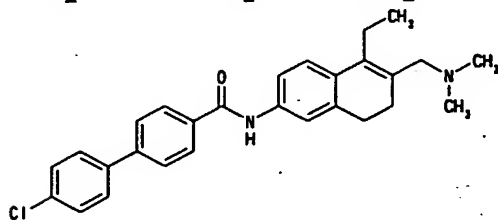
Calcd.: C, 75.25; H, 6.31; N, 6.50.

Found: C, 74.86; H, 6.20; N, 6.42.

Melting point: 199 - 204°C (crystallization solvent : diisopropyl ether)

Example 112

4'-Chloro-N-[6-[(dimethylamino)methyl]-5-ethyl-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-[(dimethylamino)methyl]-5-ethyl-7,8-dihydro-2-naphthalenamine obtained in Reference Example 67.

¹H-NMR (CDCl₃) δ: 1.09 (3H, t, J=7.5 Hz), 2.27 (6H, s), 2.31-2.37 (2H, m), 2.60-2.63 (2H, m), 2.71-2.76 (2H, m), 3.08 (2H, s), 7.31 (1H, d, J=9.2 Hz), 7.43-7.49 (4H, m),

7.56 (2H, d, J=8.7 Hz), 7.67 (2H, d, J=8.6 Hz), 7.80 (1H, s), 7.94 (2H, d, J=8.6 Hz).

Elemental analysis for $C_{28}H_{29}ClN_2O$

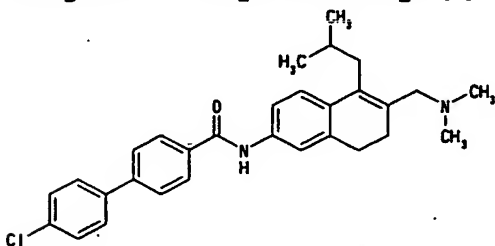
Calcd.: C, 75.57; H, 6.57; N, 6.30.

5 Found: C, 75.41; H, 6.34; N, 6.23.

Melting point: 201 - 204°C (crystallization solvent : diisopropyl ether)

Example 113

10 4'-Chloro-N-[6-[(dimethylamino)methyl]-5-isobutyl-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-

15 [6-[(dimethylamino)methyl]-5-isobutyl-7,8-dihydro-2-naphthalenamine obtained in Reference Example 68.

¹H-NMR (CDCl₃) δ: 0.90 (6H, d, J=6.4 Hz), 1.73-1.78 (1H, m), 2.23 (6H, s), 2.34 (2H, m), 2.50 (2H, d, J=7.3 Hz), 2.74 (2H, m), 3.13 (2H, s), 7.26-7.30 (1H, m), 7.45-7.48
20 (4H, m), 7.56 (2H, d, J=8.7 Hz), 7.67 (2H, d, J=8.4 Hz), 7.79 (1H, s), 7.94 (2H, d, J=8.4 Hz).

Elemental analysis for $C_{30}H_{33}ClN_2O$

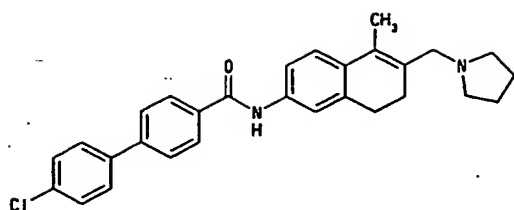
Calcd.: C, 76.17; H, 7.03; N, 5.92.

Found: C, 75.91; H, 7.19; N, 5.72.

25 Melting point: 159 - 162°C (crystallization solvent : diisopropyl ether)

Example 114

30 4'-Chloro-N-[5-methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 5-methyl-6- (1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine

5 obtained in Reference Example 69.

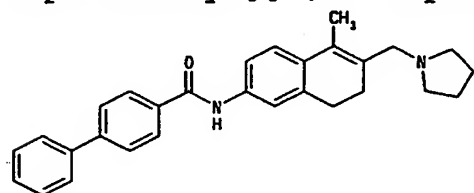
¹H-NMR (CDCl₃) δ: 1.79 (4H, m), 2.11 (3H, s), 2.30-2.40 (2H, m), 2.54 (4H, m), 2.74-2.79 (2H, m), 3.28 (2H, s), 7.26-7.30 (1H, m), 7.45-7.48 (4H, m), 7.56 (2H, d, J=8.6 Hz), 7.67 (2H, d, J=8.4 Hz), 7.81 (1H, s), 7.95 (2H, d, J=8.4 Hz).

10

Melting point: 190 - 192°C (crystallization solvent : diisopropyl ether)

Example 115

15 N-[5-Methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 5-methyl-6- (1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine

20

obtained in Reference Example 69.

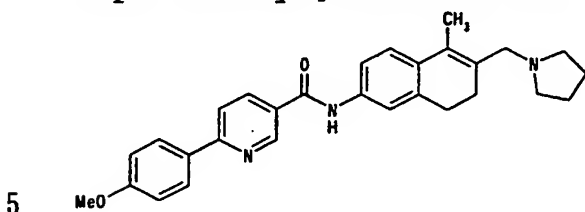
¹H-NMR (CDCl₃) δ: 1.78 (4H, m), 2.10 (3H, s), 2.35-2.40 (2H, m), 2.53 (4H, m), 2.70-2.78 (2H, m), 3.28 (2H, s), 7.26-7.28 (1H, m), 7.40-7.50 (5H, m), 7.62 (2H, d, J=7.0 Hz), 7.70 (2H, d, J=8.4 Hz), 7.87 (1H, s), 7.94 (2H, d, J=8.4 Hz).

25

Melting point: 169 - 170°C (crystallization solvent : diisopropyl ether)

Example 116

6-(4-Methoxyphenyl)-N-[5-methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]nicotinamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 5-methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 69.

10 ¹H-NMR (CDCl₃) δ: 1.78 (4H, m), 2.09 (3H, s), 2.35-2.40 (2H, m), 2.53 (4H, m), 2.70-2.77 (2H, m), 3.27 (2H, s), 3.88 (3H, s), 7.01 (2H, d, J=8.9 Hz), 7.26 (1H, d, J=8.9 Hz), 7.45-7.47 (2H, m), 7.75 (1H, d, J=8.4 Hz), 7.95 (1H, s), 8.01 (2H, d, J=8.9 Hz), 8.18-8.21 (1H, m), 9.09 (1H, m).

15 Elemental analysis for C₂₉H₃₁N₃O₂

Calcd.: C, 76.79; H, 6.89; N, 9.26.

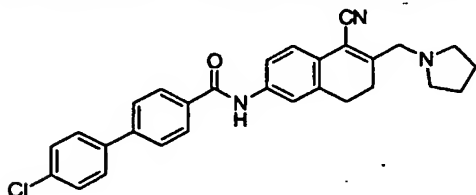
Found: C, 76.46; H, 6.64; N, 9.09.

Melting point: 165 - 167°C (crystallization solvent : diisopropyl ether)

20

Example 117

4'-Chloro-N-[5-cyano-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



25

The titled compound was obtained as a colorless powder by carrying out the same operation as in Example 1, using 6-amino-2-(1-pyrrolidinylmethyl)-3,4-dihydro-1-naphthalenecarbonitrile obtained in Reference Example 70 and 4'-chloro[1,1'-biphenyl]-4-carboxylic acid.

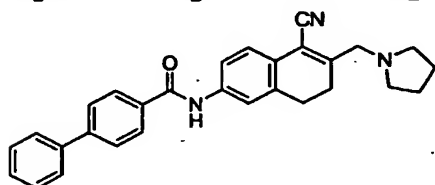
^1H NMR ($\text{DMSO}-d_6$) δ : 1.73 (4H, m), 2.50 (4H, m), 2.56 (2H, m), 2.82 (2H, m), 3.49 (2H, s), 7.32 (1H, d, $J = 9.0$ Hz), 7.57 (2H, d, $J = 8.4$ Hz), 7.56-7.87 (6H, m), 8.07 (2H, d, $J = 8.4$ Hz), 10.40 (1H, s).

5 FABMS(pos) 468.2 $[\text{M}+\text{H}]^+$

Melting point: 191 - 192°C (crystallization solvent : diisopropyl ether)

Example 118

10 N-[5-Cyano-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by as a colorless powder carrying out the same operation as in Example 1, using 6-amino-2-(1-pyrrolidinylmethyl)-3,4-dihydro-1-naphthalenecarbonitrile obtained in Reference Example 70 and [1,1'-biphenyl]-4-carboxylic acid.

15 ^1H NMR ($\text{DMSO}-d_6$) δ : 1.81 (4H, m), 2.62 (6H, m), 2.88 (2H, m), 3.56 (2H, s), 7.41 (2H, m), 7.46 (3H, m), 7.64 (2H, d, $J = 6.9$ Hz), 7.73 (3H, m), 7.88 (1H, s), 7.95 (2H, d, $J = 8.1$ Hz).

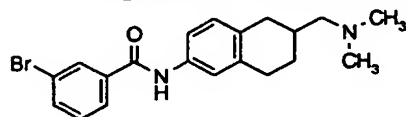
20 FABMS(pos) 434.2 $[\text{M}+\text{H}]^+$

Melting point: 168 - 170°C (crystallization solvent : diisopropyl ether)

25

Example 119

3-Bromo-N-[6-[(dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]benzamide



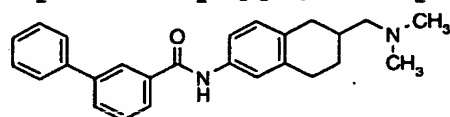
30 The titled compound was obtained by carrying out the same operation as in Example 1, using 6-amino-2-[(N,N-

dimethylamino)methyl]tetralin and 3-bromobenzoic acid.

¹H NMR (DMSO-d₆) δ: 1.31 (1H, m), 1.89 (2H, m), 2.17 (6H, s), 2.17-2.35 (3H, m), 2.77 (3H, m), 7.04 (1H, d, J=8.4 Hz), 7.49 (3H, m), 7.79 (1H, d, J=8.1 Hz), 7.94 (1H, d, J=7.8 Hz), 8.13 (1H, s), 10.20 (1H, s).

Example 120

N-[6-[(Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-3-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 16, using 3-bromo-N-[6-[(dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]benzamide obtained in Example 119 and phenylboronic acid.

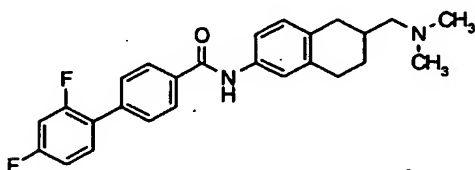
¹H NMR (DMSO-d₆) δ: 1.43 (1H, m), 2.02 (1H, m), 2.21 (1H, m), 2.42 (1H, m), 2.81 (6H, s), 2.88 (3H, m), 3.09 (2H, m), 7.06 (1H, m), 7.42-7.65 (6H, m), 7.78-7.95 (4H, m), 8.22 (1H, s), 10.27 (1H, s).

FABMS(pos) 385.2 [M+H]⁺

Melting point: 145 - 148°C (crystallization solvent : ethyl acetate-diisopropyl ether)

Example 121

N-[6-[(Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-2',4'-difluoro[1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-amino-2-[(N,N-dimethylamino)methyl]tetralin and 2',4'-difluoro[1,1'-

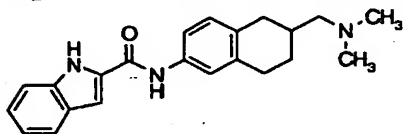
biphenyl]-4-carboxylic acid.

¹H NMR (CDCl₃) δ: 1.41 (1H, m), 1.94 (2H, m), 2.25 (6H, s),
2.23-2.30 (3H, m), 2.86 (3H, m), 6.96 (2H, m), 7.09 (1H,
d, J=8.1 Hz), 7.30 (1H, m), 7.43 (2H, m), 7.61 (2H, m), 7.76
5 (1H, s), 7.93 (2H, m).

Melting point: 162 - 163°C (crystallization solvent :
ethyl acetate-diisopropyl ether)

Example 122

10 N-[6-[(Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-1H-indole-2-carboxamide



The titled compound was obtained by carrying out the
same operation as in Example 1, using 6-amino-2-[(N,N-
15 dimethylamino)methyl]tetralin and 1H-indol-2-carboxylic
acid.

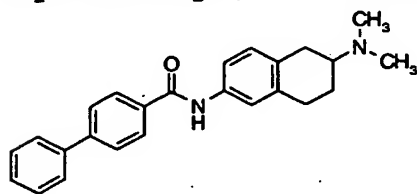
¹H NMR (DMSO-d₆) δ: 1.32 (1H, m), 1.91 (2H, m), 2.16 (6H,
s), 2.16-2.35 (3H, m), 2.78 (3H, m), 7.06 (2H, m), 7.21 (1H,
m), 7.44 (4H, m), 7.66 (1H, d, J=8.1 Hz), 10.05 (1H, s),
20 11.68 (1H, s).

FABMS(pos) 348.2 [M+H]⁺

Melting point: 190 - 192°C (crystallization solvent :
ethyl acetate - diisopropyl ether)

25 Example 123

N-[6-[(Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl] [1,1'-biphenyl]-4-carboxamide

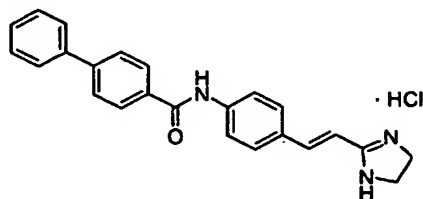


A tetrahydrofuran solution (0.146ml, 0.293mmol) of
30 N-(6-oxo-5,6,7,8-tetrahydro-2-naphthalenyl)[1,1'-

biphenyl]-4-carboxamide (10 mg, 0.029 mmol) obtained in Reference Example 72 and 2N dimethylamine was added to acetic acid-tetrahydrofuran (1:1) solution (0.5ml), which was stirred at 50°C for 15 minutes. After the reaction mixture was cooled at room temperature, sodium triacetoxhydroborate (31 mg, 0.146 mmol) was added, which was stirred at 50°C for 2 hours. 1N Hydrochloric acid was added to the reaction mixture, which was washed with ethyl acetate. Sodium carbonate was added to the water layer to make it alkaline, then extraction was conducted using ethyl acetate. The extract was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The resulting residue was purified by alumina B column chromatography (development solvent; ethyl acetate), to give the titled compound (1.6mg).
¹H NMR (CDCl₃) δ: 1.68 (1H, m), 2.27 (1H, m), 2.40 (6H, s), 2.78 (5H, m), 7.11 (1H, d, J=8.1 Hz), 7.32-7.50 (5H, m), 7.62 (2H, m), 7.72 (2H, d, J=8.4 Hz), 7.78 (1H, br), 7.94 (2H, d, J=8.4 Hz).
FABMS(pos) 371.2 [M+H]⁺

Example 124

N-[4-[(E)-2-(4,5-Dihydro-1H-imidazol-2-yl)ethenyl]phenyl]phenyl][1,1'-biphenyl]-4-carboxamide hydrochloride

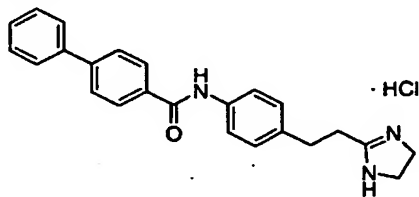


10.1 N Hydrogen chloride-ethanol solution (30 ml) was added to an ethanol suspension of N-[4-[(E)-2-cyanoethenyl]phenyl][1,1'-biphenyl]-4-carboxamide (250 mg, 0.771 mmol) obtained in Reference Example under room temperature, which was stirred for 16 hours. After the

- solvent was distilled out under reduced pressure, ethanol was again added to the residue, and then ethylenediamine (0.155 ml, 2.31 mmol) was added at room temperature, which was stirred for 16 hours. Sodium hydrogencarbonate solution was added to the reaction mixture, and the precipitated crude product was washed with water and chloroform. This product was dissolved in methanol. 1 N Hydrochloric acid (4 ml) was added to the solution, and the solvent was distilled out under reduced pressure.
- Small amount of water was added to the resulting residue, to give the titled compound (124 mg) as a colorless powder. ^1H NMR (DMSO- d_6 , free base) δ : 3.33 (4H, m), 6.61 (1H, d, $J = 16.8$ Hz), 7.15 (1H, d, $J = 16.8$ Hz), 7.52 (5H, m), 7.83 (6H, m), 8.07 (2H, d, $J = 8.4$ Hz).
- Elemental analysis for $\text{C}_{24}\text{H}_{21}\text{N}_3\text{O} \cdot \text{HCl} \cdot 1.5\text{H}_2\text{O}$
Calcd.: C, 66.89; H, 5.85; N, 9.75.
Found: C, 67.16; H, 6.10; N, 10.03.

Example 125

- N-[4-[2-(4,5-Dihydro-1H-imidazol-2-yl)ethenyl]phenyl][1,1'-biphenyl]-4-carboxamide hydrochloride



- 10% Palladium - carbon (200 mg) was added to a methanol suspension of N-[4-[(E)-2-(4,5-dihydro-1H-imidazol-2-yl)ethenyl]phenyl][1,1'-biphenyl]-4-carboxamide hydrochloride (80 mg, 0.198 mmol) obtained in Example 124, which was stirred under hydrogen atmosphere at 60°C for 2 hours. After a catalyst was filtered off, the solvent was distilled out under reduced pressure. Diethyl ether was added to the resulting residue, to give the titled compound (52 mg) as a colorless powder.

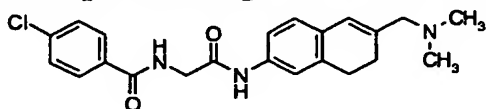
^1H NMR (DMSO- d_6) δ : 2.73-2.97 (4H, m), 3.37 (4H, s), 7.24 (2H, d, J = 8.4 Hz), 7.46 (3H, m), 7.76 (6H, m), 8.08 (2H, d, J = 8.4 Hz).

FABMS(pos) 370[M+H] $^+$

5

Example 126

4-Chloro-N-[2-[[6-[(dimethylamino)methyl]-7,8-dihydro-2-naphthalenyl]amino]-2-oxoethyl]benzamide



10 The titled compound was obtained by carrying out the same operation as in Example 1, using 6- [(N,N-dimethylamino)methyl]-7,8-dihydro-2-naphthalenamine obtained in Example 41-2) and 4-chlorobenzoyl glycine.

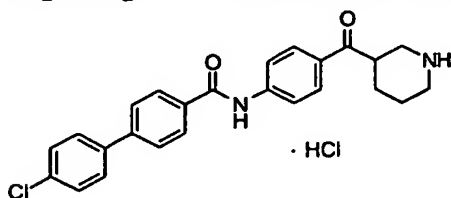
15 ^1H NMR (DMSO- d_6) δ : 2.18 (6H, s), 2.21 (2H, m), 2.71 (2H, m), 2.91 (2H, s), 4.05 (2H, d, J =5.6 Hz), 6.30 (1H, s), 6.98 (1H, d, J =8.1 Hz), 7.36 (2H, m), 7.58 (2H, d, J =8.4 Hz), 7.92 (2H, d, J =8.4 Hz), 8.94 (1H, t, J =5.6 Hz), 10.00 (1H, s).

FABMS(pos) 398 [M+H] $^+$

20 Melting point: 168 - 171°C (crystallization solvent : diisopropyl ether)

Example 127

25 4'-Chloro-N-[4-(3-piperidinylcarbonyl)phenyl][1,1'-biphenyl]-4-carboxamide hydrochloride



30 1) tert-Butyl 3-[4-[[4'-chloro[1,1'-biphenyl]-4-yl)carbonyl]amino]benzoyl]-1-piperidinecarboxylate was obtained by carrying out the same operation as in Example 1, using tert-butyl 3-(4-aminobenzoyl)-1-piperidinecarboxylate obtained in Reference Example 77 and

4'-chloro[1,1'-biphenyl]-4-carboxylic acid.

FABMS(pos) 519.2 [M+H]⁺

2) 4N Hydrogen chloride-ethyl acetate (1 ml) was added to tert-butyl 3-[4-[[[(4'-chloro[1,1'-biphenyl]-4-yl)carbonyl]amino]benzoyl]-1-piperidinecarboxylate (100 mg, 0.193 mmol) obtained in 1). One hour later, the solvent was distilled out under reduced pressure. Diisopropyl ether was added to the residue, to give the titled compound (73.3 mg) as a colorless powder.

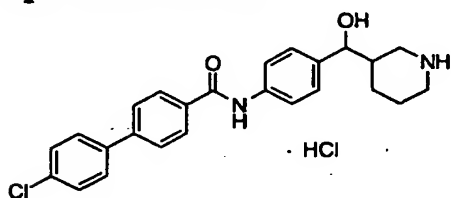
¹H NMR (DMSO-d₆) δ : 1.56 (1H, m), 1.82 (2H, m), 2.02 (1H, m), 2.89 (1H, m), 3.05 (1H, m), 3.33 (2H, m), 3.90 (1H, m), 7.58 (2H, d, J=8.1Hz), 7.81 (2H, d, J=8.1Hz), 7.88 (2H, d, J=8.1Hz), 8.03 (4H, m), 8.11 (2H, d, J=8.1Hz), 9.04 (2H, br), 10.73 (1H, s).

FABMS(pos) 419.2 [M+H]⁺

Melting point: 222 - 225°C (decomposition)

Example 128

4'-Chloro-N-[4-[hydroxy(3-piperidiny)methyl]phenyl][1,1'-biphenyl]-4-carboxamide hydrochloride



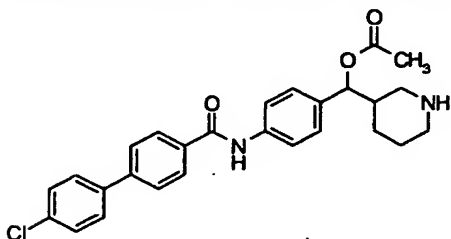
4N Hydrogen chloride-ethyl acetate (1 ml) was added to tert-butyl 3-[4-[[[(4'-chloro[1,1'-biphenyl]-4-yl)carbonyl]amino]phenyl](hydroxy)methyl]-1-piperidinecarboxylate (100 mg, 0.192 mmol) obtained in Reference Example 78. One hour later, the solvent was distilled out under reduced pressure. Diisopropyl ether was added to the residue, to give the titled compound (79.8 mg) as a colorless powder.

FABMSMS(pos) 421.2 [M+H]⁺

Melting point: 195°C (decomposition)

Example 129

[4-[[[(4'-Chloro[1,1'-biphenyl]-4-yl)carbonyl]amino]phenyl](3-piperidiny)methyl acetate



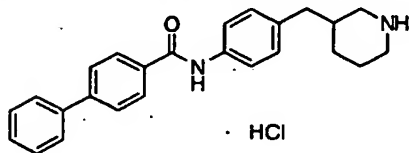
Concentrated sulfuric acid (0.0562 ml) was added to an acetic acid solution (3.5 ml) of tert-butyl 3-[[4-[[[(4'-chloro[1,1'-biphenyl]-4-yl)carbonyl]amino]phenyl](hydroxy)methyl]-1-piperidinecarboxylate (366 mg, 0.702 mmol) obtained in Example 128, which was stirred under room temperature for 16 hours. Ethyl acetate was added to the reaction mixture, which was washed with potassium hydrogencarbonate solution and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The resulting oily substance was purified by alumina B column chromatography (development solvent; ethyl acetate: methanol = 3:1), and powdered with diisopropyl ether, to give the titled compound (210 mg).

FABMS(pos) 403.2 [M+H]⁺

Melting point: 200 - 203°C.

Example 130

N-[4-(3-Piperidinylmethyl)phenyl][1,1'-biphenyl]-4-carboxamide hydrochloride

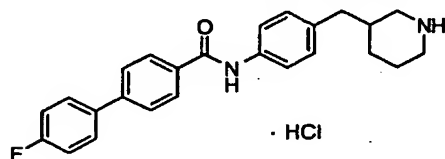


4N Hydrogen chloride-ethyl acetate (2 ml) was added to tert-butyl 3-[4-[[[1,1'-biiphenyl]-4-

ylcarbonyl)amino]benzyl]-1-piperidinecarboxylate (100 mg, 0.212 mmol) obtained in Reference Example 80. Two hours later, the solvent was distilled out under reduced pressure. Diisopropyl ether was added to the residue for
5 powdering, to give the titled compound (79 mg).
FABMS(pos) 371.3 [M+H]⁺
Melting point: 218 - 220°C (decomposition)

Example 131

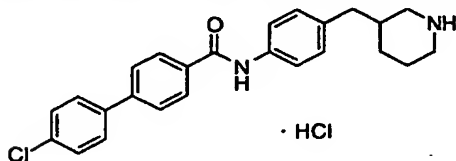
10 4'-Fluoro-N-[4-(3-piperidinylmethyl)phenyl][1,1'-biphenyl]-4-carboxamide hydrochloride



4N Hydrogen chloride-ethyl acetate (3 ml) was added to tert-butyl 3-[4-[[[4'-fluoro[1,1'-biphenyl]-4-yl)carbonyl]amino]benzyl]-1-piperidinecarboxylate (150
15 mg, 0.307 mmol) obtained in Reference Example 81. Two hours later, the solvent was distilled out under reduced pressure. Diisopropyl ether was added to the residue, to give the titled compound (115 mg) as a colorless powder.
20 FABMS(pos) 389.3 [M+H]⁺
Melting point: 205°C (decomposition)

Example 132

25 4'-Chloro-N-[4-(3-piperidinylmethyl)phenyl][1,1'-biphenyl]-4-carboxamide hydrochloride



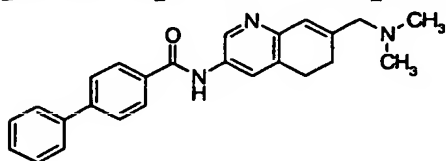
4N Hydrogen chloride-ethyl acetate (3 ml) was added to tert-butyl 3-[4-[[[4'-chloro[1,1'-biphenyl]-4-yl)carbonyl]amino]benzyl]-1-piperidinecarboxylate (150
30 mg, 0.297 mmol) obtained in Reference Example 82. Two hours

later, the solvent was distilled out under reduced pressure. Diisopropyl ether was added to the residue, to give the titled compound (73.3 mg) as a colorless powder. FABMS(pos) 405.2 [M+H]⁺

5 Melting point: 200°C (decomposition)

Example 133

N-[7-[(Dimethylamino)methyl]-5,6-dihydro-3-quinoliny][1,1'-biphenyl]-4-carboxamide



10

The titled compound was obtained by carrying out the same operation as in Example 1, using N-[(3-amino-5,6-dihydro-7-quinoliny)methyl]-N,N-dimethylamine obtained in Reference Example 86 and [1,1'-biphenyl]-4-carboxylic acid.

15

¹H NMR (DMSO-d₆) δ : 2.16 (6H, s), 2.29 (2H, t, J=8.1 Hz), 2.84 (2H, t, J=8.1 Hz), 2.98 (2H, s), 6.40 (1H, s), 7.42 (1H, m), 7.51 (2H, m), 7.76 (2H, d, J=7.2 Hz), 7.84 (2H, d, J=8.1 Hz), 7.97 (1H, s), 8.06 (2H, d, J=8.4 Hz), 8.65 (1H, s), 10.39 (1H, s).

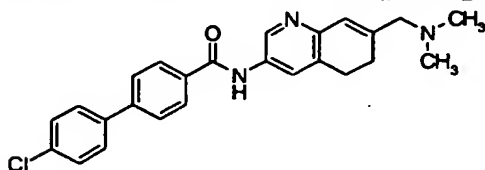
20

FABMS(pos) 384.2 [M+H]⁺

Melting point: 202 - 203°C.

Example 134

25 4'-Chloro-N-[7-[(dimethylamino)methyl]-5,6-dihydro-3-quinoliny][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using N-[(3-amino-5,6-dihydro-7-quinoliny)methyl]-N,N-dimethylamine obtained

30

in Reference Example 86 and 4'-chloro[1,1'-biphenyl]-4-carboxylic acid.

¹H NMR (DMSO-d₆) δ: 2.17 (6H, s), 2.31 (2H, t, J=8.1 Hz), 2.85 (2H, t, J=8.1 Hz), 2.99 (2H, s), 6.41 (1H, s), 7.57 (2H, d, J=8.4 Hz), 7.81 (2H, d, J=8.4 Hz), 7.86 (2H, d, J=8.4 Hz), 7.98 (1H, s), 8.08 (2H, d, J=8.4 Hz), 8.66 (1H, s), 10.41 (1H, s).

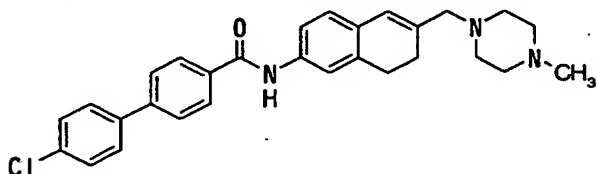
FABMS(pos) 418.2 [M+H]⁺

Melting point: 220 - 222°C.

10

Example 135

4'-Chloro-N-[6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



15

The titled compound was obtained by carrying out the same operation as in Example 51, using 4'-chloro-N-[6-(chloromethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide obtained in Reference Example 56.

¹H-NMR (CDCl₃) δ : 2.30 (3H, s), 2.25-2.50 (10H, m), 2.83 (2H, t, J = 8.1 Hz), 3.07 (2H, s), 6.35 (1H, s), 7.01 (1H, d, J = 8.1 Hz), 7.36 (1H, d, J = 7.8 Hz), 7.44 (2H, d, J = 8.4 Hz), 7.51 (1H, s), 7.55 (2H, d, J = 8.4 Hz), 7.66 (2H, d, J = 8.4 Hz), 7.84 (1H, s), 7.93 (2H, d, J = 8.4 Hz).

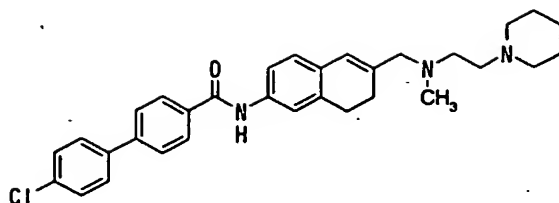
Melting point: 220 - 222°C (crystallization solvent : tetrahydrofuran - n-hexane)

25

Example 136

4'-Chloro-N-[6-[[methyl[2-(1-piperidinyl)ethyl]amino]methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide

30



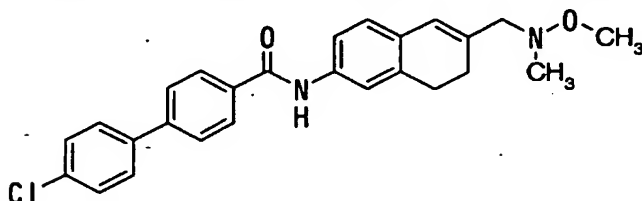
The titled compound was obtained by carrying out the same operation as in Example 51, using 4'-chloro-N-[6-(chloromethyl)-7,8-dihydro-2-naphthalenyl][1,1'-

- 5 biphenyl]-4-carboxamide obtained in Reference Example 56.
¹H-NMR (CDCl₃) δ : 1.72-1.77 (6H, m), 2.25-2.36 (2H, m), 2.27 (3H, s), 2.52-2.63 (8H, m), 2.84 (2H, t, J = 8.0 Hz), 3.08 (2H, s), 6.35 (1H, s), 7.01 (1H, d, J = 8.1 Hz), 7.38 (1H, d, J = 8.1 Hz), 7.44 (2H, d, J = 8.4 Hz), 7.49 (1H, s),
 10 s), 7.55 (2H, d, J = 8.4 Hz), 7.66 (2H, d, J = 8.4 Hz), 7.83 (1H, s), 7.93 (2H, d, J = 8.4 Hz).

Melting point: 165 - 167°C (crystallization solvent -: tetrahydrofuran - n-hexane)

15 Example 137

4'-Chloro-N-[6-[[methoxy(methyl)amino]methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



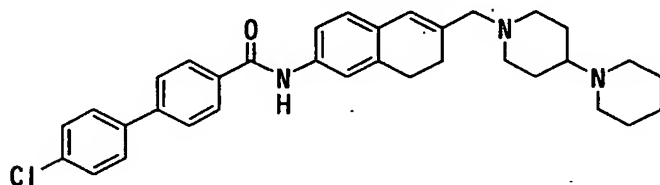
- 20 The titled compound was obtained by carrying out the same operation as in Example 51, using 4'-chloro-N-[6-(chloromethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide obtained in Reference Example 56.

- ¹H-NMR (CDCl₃) δ : 2.41 (2H, t, J = 8.1 Hz), 2.61 (3H, s), 2.86 (2H, t, J = 8.1 Hz), 3.37 (2H, s), 3.52 (3H, s), 6.39 (1H, s), 7.03 (1H, d, J = 8.1 Hz), 7.36 (1H, d, J = 8.1 Hz),
 25 7.44 (2H, d, J = 8.4 Hz), 7.53 (1H, s), 7.55 (2H, d, J = 8.4 Hz), 7.66 (2H, d, J = 8.4 Hz), 7.83 (1H, s), 7.93 (2H, d, J = 8.4 Hz).

Melting point: 190 - 192°C (crystallization solvent :
ethyl acetate - n-hexane)

Example 138

- 5 4'-Chloro-N-[6-[[4-(1-piperidiny1)-1-piperidiny1]methyl]-7,8-dihydro-2-naphthaleny1][1,1'-bipheny1]-4-carboxamide

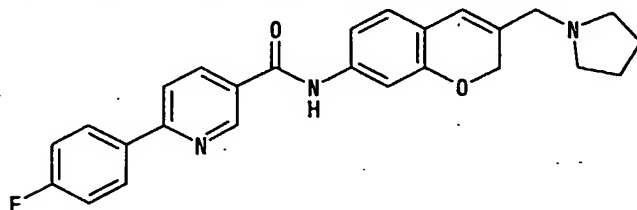


- The titled compound was obtained by carrying out the
10 same operation as in Example 51, using 4'-chloro-N-[6-(chloromethyl)-7,8-dihydro-2-naphthaleny1][1,1'-bipheny1]-4-carboxamide obtained in Reference Example 56.
¹H-NMR (CDCl₃) δ : 1.45-1.96 (12H, m), 2.29-2.34 (3H, m),
2.57 (4H, s), 2.83 (2H, t, J = 8.1 Hz), 2.96-3.03 (4H, m),
15 6.32 (1H, s), 7.00 (1H, d, J = 8.1 Hz), 7.38 (1H, d, J = 8.1 Hz), 7.44 (2H, d, J = 8.4 Hz), 7.50 (1H, s), 7.55 (2H, d, J = 8.4 Hz), 7.66 (2H, d, J = 8.4 Hz), 7.86 (1H, s), 7.93 (2H, d, J = 8.4 Hz).

- Melting point: 232 - 234°C (crystallization solvent :
20 ethyl acetate - n-hexane)

Example 139

6-(4-Fluoropheny1)-N-[3-(1-pyrrolidiny1methyl)-2H-chromen-7-yl]nicotineamide



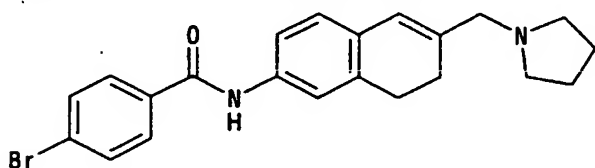
- 25 The titled compound was obtained by carrying out the same operation as in Example 1, using 3-(1-pyrrolidiny1methyl)-2H-chromen-7-amine obtained in Reference Example 87.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.70 (4H, s), 2.43 (4H, s), 3.12 (2H, s), 4.73 (2H, s), 6.37 (1H, s), 7.03 (1H, d, $J = 7.8$ Hz), 7.29-7.40 (4H, m), 8.15 (1H, d, $J = 8.4$ Hz), 8.22-8.39 (3H, m), 9.15 (1H, s), 10.40 (1H, s).

- 5 Melting point: 233 - 235°C (crystallization solvent : tetrahydrofuran - n-hexane)

Example 140

- 10 4-Bromo-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]benzamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine

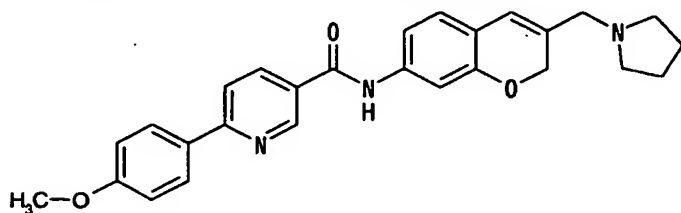
- 15 obtained in Reference Example 54.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.79 (4H, s), 2.35 (2H, t, $J = 8.1$ Hz), 2.52 (4H, s), 2.83 (2H, t, $J = 8.1$ Hz), 3.17 (2H, s), 6.35 (1H, s), 6.99 (1H, d, $J = 8.1$ Hz), 7.34 (1H, d, $J = 8.1$ Hz), 7.43 (1H, s), 7.60 (2H, d, $J = 8.4$ Hz), 7.72 (2H, d, $J = 8.4$ Hz), 7.76 (1H, s).

20 Melting point: 135 - 137°C (crystallization solvent : ethyl acetate - n-hexane)

Example 141

- 25 6-(4-Methoxyphenyl)-N-[3-(1-pyrrolidinylmethyl)-2H-chromen-7-yl]nicotinamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 3-(1-

pyrrolidinylmethyl)-2H-chromen-7-amine obtained in Reference Example 87.

¹H-NMR (CDCl₃) δ : 1.70 (4H, s), 2.44 (4H, s), 3.12 (2H, s), 3.84 (3H, s), 4.73 (2H, s), 6.37 (1H, s), 7.03 (1H, d, J = 8.1 Hz), 7.09 (2H, t, J = 8.7 Hz), 7.29 (1H, d, J = 8.4 Hz), 7.31 (1H, s), 8.07 (1H, d, J = 8.7 Hz), 8.16 (2H, d, J = 8.7 Hz), 8.32 (1H, d, J = 8.4 Hz), 9.12 (1H, s), 10.34 (1H, s).

Elemental analysis for C₂₇H₂₇N₃O₃

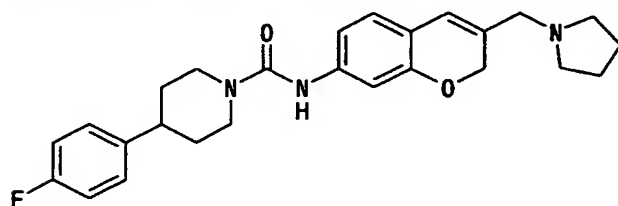
10 Calcd.: C, 73.45; H, 6.16; N, 9.52.

Found: C, 73.02; H, 6.27; N, 9.33.

Melting point: 243 - 245°C (crystallization solvent : tetrahydrofuran - n-hexane)

15 Example 142

4-(4-Fluorophenyl)-N-[3-(1-pyrrolidinylmethyl)-2H-chromen-7-yl]-1-piperidinecarboxamide



20 The titled compound was obtained by carrying out the same operation as in Example 99, using 3-(1-pyrrolidinylmethyl)-2H-chromen-7-amine obtained in Reference Example 87.

¹H-NMR (CDCl₃) δ : 1.69- 1.91 (8H, m), 2.49 (4H, s), 2.70 (1H, t, J = 12.0 Hz), 2.97 (2H, t, J = 12.0 Hz), 3.12 (2H, s), 4.19 (2H, d, J = 13.0 Hz), 4.76 (2H, s), 6.26 (1H, s), 6.37 (1H, s), 6.82-7.03 (5H, m), 7.16 (2H, dd, J = 5.4, 8.4 Hz).

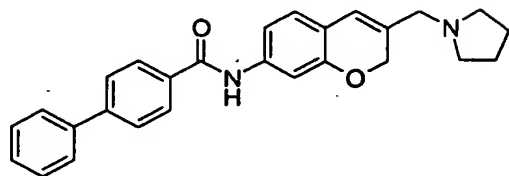
Melting point: 176 - 178°C (crystallization solvent : ethyl acetate - diisopropyl ether)

30

Example 143

N-[3-(1-Pyrrolidinylmethyl)-2H-chromen-7-yl][1,1'-

biphenyl]-4-carboxamide

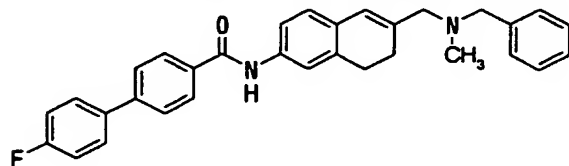


The titled compound was obtained by carrying out the same operation as in Example 1, using 3-(1-pyrrolidinylmethyl)-2H-chromen-7-amine obtained in Reference Example 87.

¹H-NMR (CDCl₃) δ : 1.79 (4H, s), 2.50 (4H, s), 3.15 (2H, s), 4.81 (2H, s), 6.30 (1H, s), 6.95 (1H, d, J = 8.1 Hz), 7.13 (1H, s), 7.20 (1H, d, J = 8.1 Hz), 7.39-7.50 (3H, m), 7.61-7.70 (4H, m), 7.82 (1H, s), 7.92 (2H, d, J = 8.1 Hz).
Melting point: 198 - 200°C (crystallization solvent : ethyl acetate)

Example 144

N-[6-[(N-Benzyl-N-methylamino)methyl]-7,8-dihydro-2-naphthalenyl]-4'-fluoro[1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-[(N-benzyl-N-methylamino)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 88.

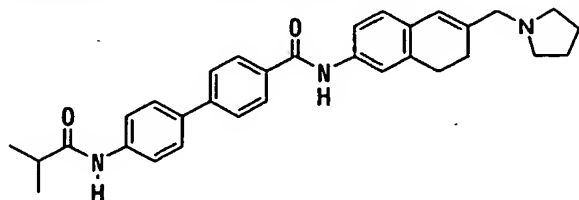
¹H-NMR (CDCl₃) δ : 2.20 (3H, s), 2.38 (2H, t, J = 8.1 Hz), 2.85 (2H, t, J = 8.1 Hz), 3.09 (2H, s), 3.52 (2H, s), 6.39 (1H, s), 7.02 (1H, d, J = 8.1 Hz), 7.13-7.66 (13H, m), 7.84 (1H, s), 7.93 (2H, d, J = 8.4 Hz).

Melting point: 143 - 145°C (crystallization solvent : ethyl acetate - n-hexane)

Example 145

4'-Isobutyrylamino-N-[6-(1-pyrrolidinylmethyl)-7,8-

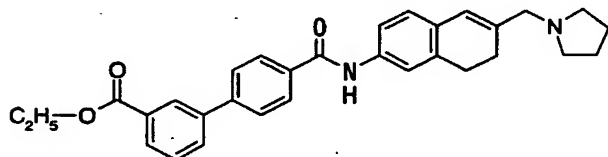
dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained as an amorphous powder by carrying out the same operation as in Example 1, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54. MS m/z 494.4 (MH⁺).

Example 146

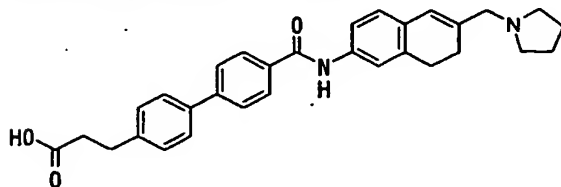
Ethyl 4'-[[[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]amino]carbonyl][1,1'-biphenyl]-3-carboxylate



The titled compound was obtained as an amorphous powder by carrying out the same operation as in Example 1, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54. MS m/z 481.4 (MH⁺).

Example 147

3-[4'-[[[6-(1-Pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]amino]carbonyl][1,1'-biphenyl]-4-yl]propionic acid



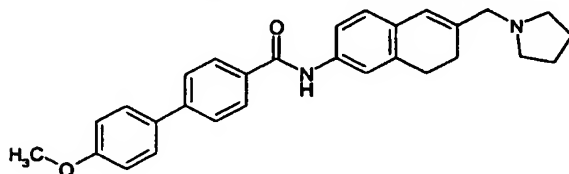
The titled compound was obtained as a powder by carrying out the same operation as in Example 1, using

6-(1-pyrrolidinymethyl)-7,8--dihydro-2-naphthalenamine
obtained in Reference Example 54.

MS m/z 481.4 (MH^+).

5 Example 148

4'-Methoxy-N-[6-(1-pyrrolidinymethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



10 The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(1-pyrrolidinymethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

1H -NMR ($CDCl_3$) δ : 1.80 (4H, m), 2.36 (2H, t, $J=7.8$ Hz), 2.52 (4H, m), 2.86 (2H, t, $J=7.8$ Hz), 3.18 (2H, s), 3.87 (3H, s), 6.36 (1H, s), 7.00-7.03 (3H, m), 7.26 (1H, m), 7.38 (1H, d, $J=8.3$ Hz), 7.49 (1H, s), 7.58 (2H, d, $J=8.6$ Hz), 7.67 (1H, d, $J=8.2$ Hz), 7.78 (1H, s), 7.90 (2H, d, $J=8.2$ Hz).

Elemental analysis for $C_{29}H_{30}N_2O_2$

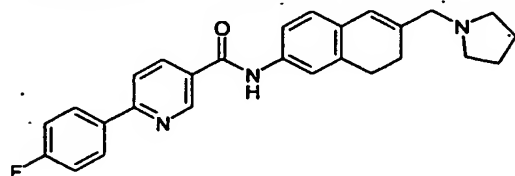
Calcd.: C, 79.42; H, 6.89; N, 6.39.

20 Found: C, 79.21; H, 6.88; N, 6.35.

Melting point: 187-188 $^{\circ}C$ (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 149

25 6-(4-Fluorophenyl)-N-[6-[(1-pyrrolidinyl)methyl]-7,8-dihydro-2-naphthalenyl]nicotinamide



30 The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(1-pyrrolidinymethyl)-7,8-dihydro-2-naphthalenamine

obtained in Reference Example 54.

¹H-NMR (CDCl₃) δ: 1.81 (4H, m), 2.36 (2H, t, J=8.1 Hz), 2.53 (4H, m), 2.86 (2H, t, J=8.1 Hz), 3.18 (2H, s), 6.37 (1H, s), 7.03 (1H, d, J=7.8 Hz), 7.16-7.30 (3H, m), 7.47 (1H, s), 7.77-7.82 (2H, m), 8.06 (2H, dd, J=8.9, 5.3 Hz), 8.25 (1H, dd, J=8.4, 2.2 Hz), 9.11 (1H, d, J=2.0 Hz).

Elemental analysis for C₂₇H₂₆N₃O

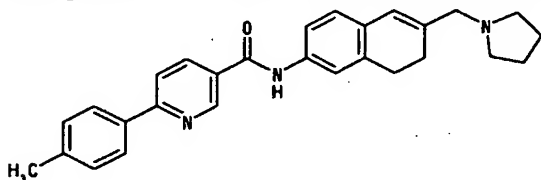
Calcd.: C, 75.85; H, 6.13; N, 9.83.

Found: C, 75.71; H, 5.93; N, 9.75.

Melting point: 225-227 °C (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 150

6-(4-Methylphenyl)-N-[6-[(1-pyrrolidinyl)methyl]-7,8-dihydro-2-naphthalenyl]nicotinamide



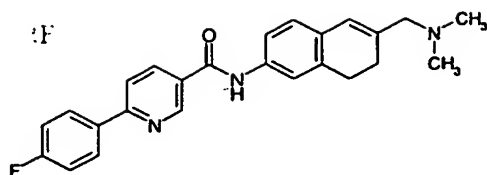
The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

¹H-NMR (CDCl₃) δ: 1.81 (4H, m), 2.36 (2H, t, J=7.8 Hz), 2.43 (3H, s), 2.53 (4H, m), 2.86 (2H, t, J=7.8 Hz), 3.19 (2H, s), 6.37 (1H, s), 7.02 (1H, d, J=8.7 Hz), 7.25-7.39 (3H, m), 7.47 (1H, s), 7.82 (2H, m), 7.96 (2H, d, J=8.1 Hz), 8.23 (1H, dd, J=8.1, 2.3 Hz), 9.12 (1H, d, J=2.3 Hz).

Melting point: 235-236 °C (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 151

N-[6-[(Dimethylamino)methyl]-7,8-dihydro-2-naphthalenyl]-6-(4-fluorophenoxy)nicotinamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-[(N,N-dimethylamino)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 41-2).

¹H-NMR (CDCl₃) δ: 2.25 (6H, s), 2.34 (2H, t, J=8.1 Hz), 2.86 (2H, t, J=8.1 Hz), 2.99 (2H, s), 6.35 (1H, s), 7.03 (1H, d, J=8.1 Hz), 7.17 (2H, m), 7.26 (1H, m), 7.39 (1H, d, J=8.1 Hz), 7.47 (1H, s), 7.78 (1H, d, J=7.2 Hz), 7.83 (1H, s), 8.06 (1H, dd, J=8.4, 6.7 Hz), 8.25 (1H, d, J=6.7 Hz), 9.12 (1H, s).

Elemental analysis for C₂₅H₂₄FN₃O

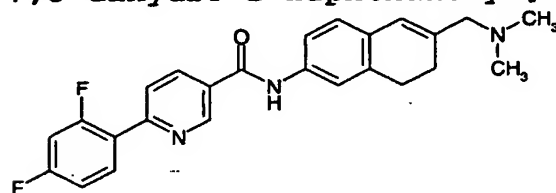
Calcd.: C, 74.79; H, 6.03; N, 10.47.

Found: C, 74.74; H, 5.95; N, 10.24.

Melting point: 216-219 °C (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 152

6-(2,4-Difluorophenyl)-N-[6-[(dimethylamino)methyl]-7,8-dihydro-2-naphthalenyl]nicotinamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-[(N,N-dimethylamino)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 41-2).

¹H-NMR (CDCl₃) δ: 2.25 (6H, s), 2.34 (2H, t, J=8.1 Hz), 2.85 (2H, t, J=8.1 Hz), 3.00 (2H, s), 6.35 (1H, s), 6.90-7.06 (3H, m), 7.39 (1H, d, J=7.8 Hz), 7.47 (1H, s), 7.80-7.90 (2H, m), 8.10 (1H, dd, J=15.3, 8.8 Hz), 8.23 (1H, dd, J=8.4, 2.3 Hz), 9.15 (1H, d, J=1.7 Hz).

Elemental analysis for $C_{25}H_{23}F_2N_3O$

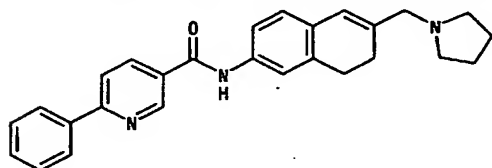
Calcd.: C, 71.58; H, 5.53; N, 10.02.

Found: C, 71.50; H, 5.49; N, 9.61.

Melting point: 162-163 °C (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 153

6-Phenyl-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]nicotinamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.81 (4H, m), 2.36 (2H, t, $J=8.1$ Hz), 2.53 (4H, m), 2.85 (2H, t, $J=8.1$ Hz), 3.18 (2H, s), 6.37 (1H, s), 7.02 (1H, d, $J=8.1$ Hz), 7.37-7.53 (5H, m), 7.83 (1H, d, $J=8.1$ Hz), 7.86 (1H, d, $J=6.2$ Hz), 8.04 (1H, s), 8.06 (1H, d, $J=1.7$ Hz), 8.24 (1H, dd, $J=8.4, 2.4$ Hz), 9.13 (1H, d, $J=2.2$ Hz).

Elemental analysis for $C_{27}H_{27}N_3O$

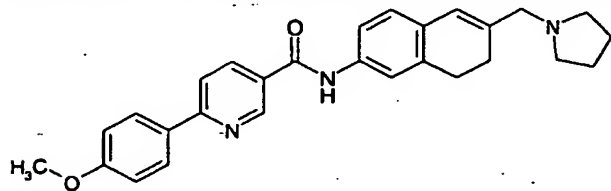
Calcd.: C, 79.19; H, 6.65; N, 10.26.

Found: C, 78.93; H, 6.65; N, 10.19.

Melting point: 186-187 °C (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 154

6-(4-Methoxyphenyl)-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]nicotinamide

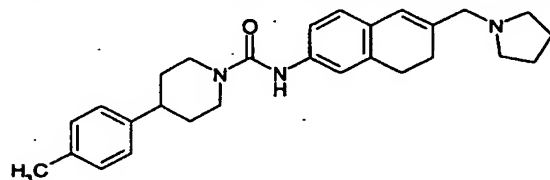


The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

- 5 ¹H-NMR (CDCl₃) δ : 1.80 (4H, m), 2.36 (2H, t, J=8.1 Hz), 2.52 (4H, m), 2.84 (2H, t, J=8.1 Hz), 3.18 (2H, s), 3.88 (3H, s), 6.36 (1H, s), 7.02 (3H, m), 7.37 (1H, d, J=7.5 Hz), 7.47 (1H, s), 7.78 (1H, d, J=8.1 Hz), 7.79 (1H, s), 8.03 (2H, d, J=8.5 Hz), 8.20 (1H, d, J=8.1 Hz), 9.08 (1H, s).
- 10 Melting point: : 219-220 °C (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 155

- 15 4-(4-Methylphenyl)-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide



The titled compound was obtained by carrying out the same operation as in Example 99, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

- 20 ¹H-NMR (CDCl₃) δ : 1.64-1.92 (8H, m), 2.29 (2H, m), 2.32 (3H, s), 2.51 (4H, m), 2.64 (1H, m), 2.80 (2H, t, J=7.8 Hz), 2.97 (2H, dd, J=13.1, 10.7 Hz), 3.15 (2H, s), 4.19 (2H, d, J=13.1 Hz), 6.32 (1H, s), 6.35 (1H, s), 6.42 (1H, d, J=7.8 Hz), 7.06-7.20 (6H, m)

25 Elemental analysis for C₂₈H₃₅N₃O · 0.5H₂O

Calcd.: C, 76.67; H, 8.27; N, 9.58.

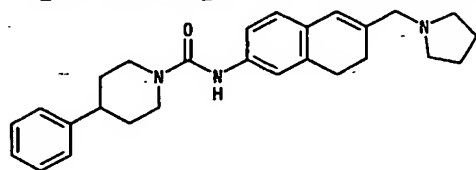
Found: C, 76.72; H, 8.03; N, 9.36.

- Melting point: 197-198 °C (crystallization solvent: ethyl acetate - diisopropyl ether)
- 30

Example 156

4-Phenyl-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-

naphthalenyl]-1-piperidinecarboxamide



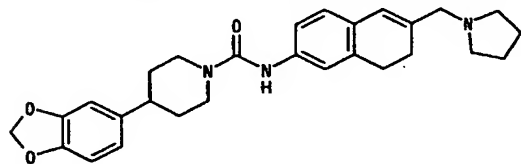
The titled compound was obtained by carrying out the same operation as in Example 99, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

¹H-NMR (CDCl₃) δ: 1.72-1.94 (8H, m), 2.32 (2H, t, J=8.1 Hz), 2.50 (4H, m), 2.72 (1H, m), 2.80 (2H, t, J=8.1 Hz), 2.99 (2H, dd, J=13.4, 10.6 Hz), 3.16 (2H, s), 4.21 (2H, d, J=13.4 Hz), 6.32 (1H, s), 6.34 (1H, s), 6.93 (1H, d, J=8.4 Hz), 7.07 (1H, d, J=8.1 Hz), 7.20-7.35 (6H, m).

Meltingpoint: 184-186 °C (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 157

4-(1,3-Benzodioxol-5-yl)-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide



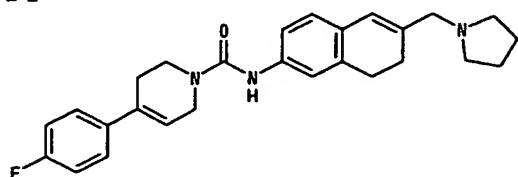
The titled compound was obtained by carrying out the same operation as in Example 99, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

¹H-NMR (CDCl₃) δ: 1.61-1.88 (8H, m), 2.31 (2H, t, J=8.1 Hz), 2.51 (4H, m), 2.59 (1H, m), 2.62 (2H, t, J=8.1 Hz), 2.94 (2H, dd, J=13.1, 11.2 Hz), 3.15 (2H, s), 4.18 (2H, d, J=13.1 Hz), 5.93 (2H, s), 6.31 (1H, s), 6.44 (1H, s), 6.64-6.77 (3H, m), 6.92 (1H, d, J=8.1 Hz), 7.07 (1H, d, J=8.1 Hz), 7.19 (1H, s).

Meltingpoint: 149-150 °C (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 158

4-(4-Fluorophenyl)-N-[6-(1-pyrrolidinymethyl)-7,8-dihydro-2-naphthalenyl]-3,6-dihydro-1(2H)-pyridinecarboxamide



The titled compound was obtained by carrying out the same operation as in Example 99, using 6-(1-pyrrolidinymethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

¹H-NMR (CDCl₃) δ: 1.79 (4H, m), 2.32 (2H, t, J=8.1 Hz), 2.50 (4H, m), 2.59 (2H, brt), 2.80 (2H, t, J=8.1 Hz), 3.17 (2H, s), 3.74 (2H, t, J=5.7 Hz), 4.15 (2H, d, J=2.5 Hz), 6.00 (1H, brt), 6.32 (1H, s), 6.32 (1H, s), 6.94 (1H, d, J=8.1 Hz), 7.00-7.32 (6H, m).

Elemental analysis for C₂₇H₃₀FN₃O

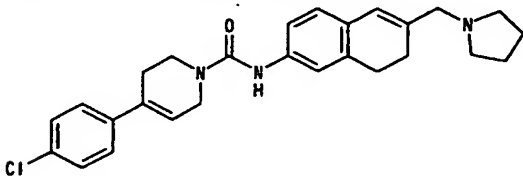
Calcd.: C, 75.15; H, 7.01; N, 9.74.

Found: C, 75.09; H, 6.93; N, 9.77.

Melting point: 206-207 °C (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 159

4-(4-Chlorophenyl)-N-[6-(1-pyrrolidinymethyl)-7,8-dihydro-2-naphthalenyl]-3,6-dihydro-1(2H)-pyridinecarboxamide



The titled compound was obtained by carrying out the same operation as in Example 99, using 6-(1-pyrrolidinymethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

¹H-NMR (CDCl₃) δ: 1.79 (4H, m), 2.32 (2H, t, J=8.1 Hz), 2.50 (4H, m), 2.59 (2H, brt), 2.80 (2H, t, J=8.1 Hz), 3.16 (2H, s), 3.73 (2H, t, J=5.6 Hz), 4.15 (2H, d, J=2.8 Hz), 6.06 (1H, brt), 6.30 (1H, s), 6.32 (1H, s), 6.93 (1H, d, J=7.8 Hz), 7.09 (1H, d, J=7.8 Hz), 7.21-7.31 (5H, m).

Elemental analysis for C₂₇H₃₀ClN₃O

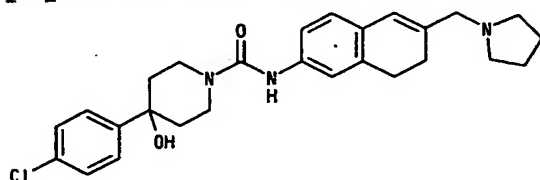
Calcd.: C, 72.39; H, 6.75; N, 9.38.

Found: C, 72.19; H, 6.75; N, 9.19.

Melting point: 217-218 °C (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 160

4-(4-Chlorophenyl)-4-hydroxy-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide



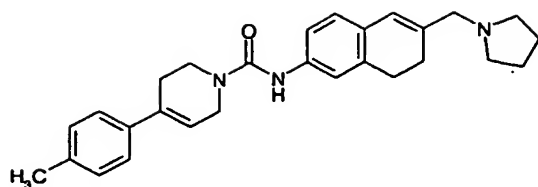
The titled compound was obtained by carrying out the same operation as in Example 99, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

¹H-NMR (CDCl₃) δ: 1.79 (4H, m), 1.80 (2H, m), 2.04 (1H, dd, J=13.1, 10.8 Hz), 2.06 (1H, dd, J=13.1, 10.8 Hz), 2.31 (2H, t, J=7.8 Hz), 2.50 (1H, brs), 2.51 (4H, m), 2.79 (2H, t, J=7.8 Hz), 3.15 (2H, s), 3.41 (2H, dd, J=12.6, 10.8 Hz), 4.00 (2H, d, J=12.6 Hz), 6.32 (1H, s), 6.37 (1H, s), 6.93 (1H, d, J=8.1 Hz), 7.05-7.42 (6H, m).

Melting point: 181-182 °C (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 161

4-(4-Methylphenyl)-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]-3,6-dihydro-1(2H)-pyridinecarboxamide



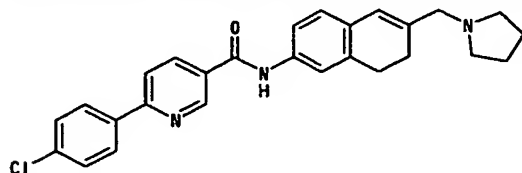
The titled compound was obtained by carrying out the same operation as in Example 99, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

¹H-NMR (CDCl₃) δ: 1.79 (4H, m), 2.32 (2H, t, J=7.8 Hz), 2.35 (3H, s), 2.50 (4H, m), 2.61 (2H, brt), 2.80 (2H, t, J=7.8 Hz), 3.16 (2H, s), 3.73 (2H, t, J=5.7 Hz), 4.15 (2H, d, J=2.8 Hz), 6.03 (1H, s), 6.29 (1H, s), 6.32 (1H, s), 6.93 (1H, d, J=8.1 Hz), 7.07-7.30 (6H, m).

Melting point: 199-202 °C (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 162

6-(4-Chlorophenyl)-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]nicotinamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

¹H-NMR (CDCl₃+DMSO-d₆) δ: 1.80 (4H, m), 2.32-2.58 (6H, m), 2.85 (2H, t, J=8.0 Hz), 3.18 (2H, s), 6.36 (1H, s), 7.01 (1H, d, J=8.4 Hz), 7.48 (2H, d, J=8.4 Hz), 7.49 (1H, m), 7.59 (1H, s), 7.83 (1H, d, J=8.4 Hz), 8.04 (2H, d, J=8.4 Hz), 8.35 (1H, dd, J=8.4, 2.2 Hz), 9.25 (1H, d, J=2.2 Hz), 9.42 (1H, s).

Elemental analysis for C₂₇H₂₆ClN₃O

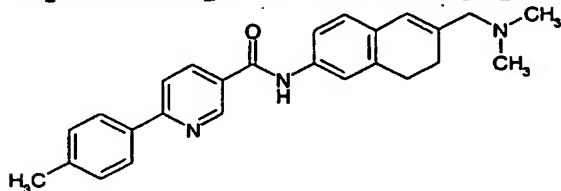
Calcd.: C, 73.04; H, 5.90; N, 9.46.

Found: C, 73.11; H, 5.71; N, 9.20.

Melting point: 252-253 °C (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 163

- 5 N-[6-[(Dimethylamino)methyl]-7,8-dihydro-2-naphthalenyl]-6-(4-methylphenyl)nicotinamide



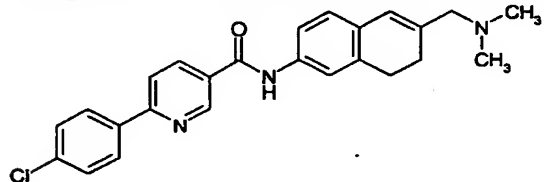
- The titled compound was obtained by carrying out the same operation as in Example 1, using 6-[(N,N-dimethylamino)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 41-2).

- ¹H-NMR (CDCl₃) δ: 2.25 (6H, s), 2.34 (2H, t, J=8.1 Hz), 2.43 (3H, s), 2.85 (2H, t, J=8.1 Hz), 2.99 (2H, s), 6.34 (1H, s), 7.02 (1H, d, J=8.1 Hz), 7.31 (2H, d, J=8.1 Hz), 7.39 (1H, d, J=8.1 Hz), 7.46 (1H, s), 7.81 (1H, d, J=8.4 Hz), 7.87 (1H, s), 7.96 (2H, d, J=8.1 Hz), 8.22 (1H, dd, J=8.4, 2.3 Hz), 9.11 (1H, d, J=2.3 Hz).

Melting point: 228-230 °C (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 164

- 6-(4-Chlorophenyl)-N-[6-[(dimethylamino)methyl]-7,8-dihydro-2-naphthalenyl]nicotinamide



- The titled compound was obtained by carrying out the same operation as in Example 1, using 6-[(N,N-dimethylamino)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 41-2).

- ¹H-NMR (CDCl₃) δ: 2.25 (6H, s), 2.35 (2H, t, J=8.1 Hz), 2.86 (2H, t, J=8.1 Hz), 2.99 (2H, s), 6.35 (1H, s), 7.04 (1H,

d, J=8.1 Hz), 7.40 (1H, d, J=8.4 Hz), 7.49 (1H, brs), 7.49 (2H, d, J=8.4 Hz), 7.78 (1H, s), 7.84 (1H, d, J=8.4 Hz), 8.02 (2H, d, J=8.4 Hz), 8.26 (1H, dd, J=8.1, 2.2 Hz), 9.13 (1H, d, J=2.2 Hz).

5 Elemental analysis for $C_{25}H_{24}ClN_3O$

Calcd.: C, 71.85; H, 5.79; N, 10.05.

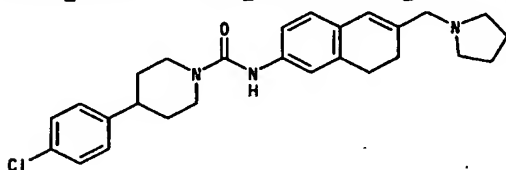
Found: C, 71.88; H, 5.67; N, 9.86.

Melting point: 248-249 °C (crystallization solvent: ethyl acetate - diisopropyl ether)

10

Example 165

4-(4-Chlorophenyl)-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide



15

The titled compound was obtained by carrying out the same operation as in Example 99, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.66-1.91 (8H, m), 2.32 (2H, t, J=8.1 Hz), 2.50 (4H, m), 2.70 (1H, m), 2.80 (2H, t, J=8.1 Hz), 2.98 (2H, dd, J=13.7, 12.0 Hz), 3.16 (2H, s), 4.20 (2H, d, J=13.7 Hz), 6.32 (1H, s), 6.32 (1H, s), 6.93 (1H, d, J=8.1 Hz), 7.05-7.30 (6H, m).

25 Elemental analysis for $C_{27}H_{32}ClN_3O$

Calcd.: C, 72.06; H, 7.17; N, 9.34.

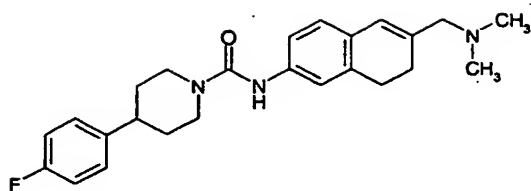
Found: C, 72.08; H, 7.23; N, 9.15.

Melting point: 194-195 °C (crystallization solvent: ethyl acetate - diisopropyl ether)

30

Example 166

N-[6-[(Dimethylamino)methyl]-7,8-dihydro-2-naphthalenyl]-4-(4-fluorophenyl)-1-piperidinecarboxamide



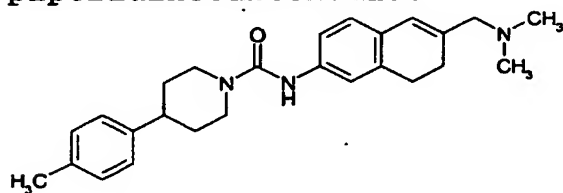
The titled compound was obtained by carrying out the same operation as in Example 99, using 6-[(N,N-dimethylamino)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 41-2).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.65-1.75 (2H, m), 1.89 (2H, d, $J=11.4$ Hz), 2.23 (6H, s), 2.30 (2H, t, $J=8.1$ Hz), 2.70 (1H, m), 2.80 (2H, t, $J=8.1$ Hz), 2.94-3.01 (4H, m), 4.20 (2H, d, $J=13.4$ Hz), 6.30 (1H, s), 6.35 (1H, s), 6.92-7.20 (7H, m).

Meltingpoint: 187-188 $^{\circ}\text{C}$ (crystallization solvent: ethyl acetate - diisopropyl ether).

Example 167

N-[6-[(Dimethylamino)methyl]-7,8-dihydro-2-naphthalenyl]-4-(4-methylphenyl)-1-piperidinecarboxamide



The titled compound was obtained by carrying out the same operation as in Example 99, using 6-[(N,N-dimethylamino)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 41-2).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.66-1.74 (2H, m), 1.89 (2H, d, $J=11.7$ Hz), 2.28 (6H, s), 2.30 (2H, t, $J=8.1$ Hz), 2.38 (3H, s), 2.68 (1H, m), 2.80 (2H, t, $J=8.1$ Hz), 2.94-3.02 (4H, m), 4.19 (2H, d, $J=12.8$ Hz), 6.30 (1H, s), 6.35 (1H, s), 6.93 (1H, d, $J=8.1$ Hz), 7.07-7.20 (6H, m).

Elemental analysis for $\text{C}_{26}\text{H}_{33}\text{N}_3\text{O} \cdot 0.5\text{H}_2\text{O}$

Calcd.: C, 75.69; H, 8.31; N, 10.18

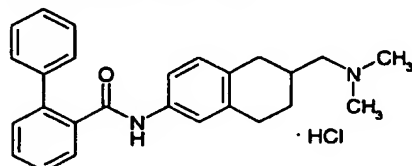
Found: C, 75.44; H, 8.16; N, 10.05

Meltingpoint: 200-202 $^{\circ}\text{C}$ (crystallization solvent: ethyl

acetate - diisopropyl ether)

Example 168

5 N-[6-[(Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-2-carboxamide hydrochloride



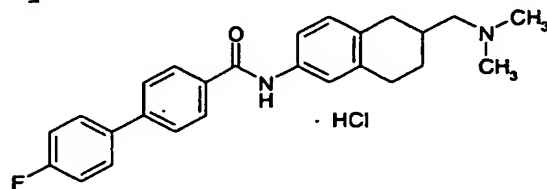
The titled compound was obtained by carrying out the same operation as in Example 1, using 6-amino-2-[(N,N-dimethylamino)methyl]tetralin hydrochloride.

10 ¹H-NMR (DMSO-d₆) δ: 1.39 (1H, m), 1.99 (1H, m), 2.17 (1H, m), 2.42 (1H, dd, J=16.2, 10.1 Hz), 2.78 (6H, s), 2.88 (1H, dd, J=16.2, 4.5 Hz), 3.06 (2H, t, J=5.7 Hz), 3.38 (2H, s), 6.94-7.62 (11H, m), 7.64 (1H, d, J=1.7 Hz), 10.11 (1H, brs), 10.18 (1H, s).

Melting point: 196-197 °C (crystallization solvent: methanol - ethyl acetate)

Example 169

20 N-[6-[(Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4'-fluoro[1,1'-biphenyl]-4-carboxamide hydrochloride



25 4'-Fluoro-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide synthesized in Example 42 was dissolved in ethyl acetate. An excess amount of 4N hydrochloric acid-ethyl acetate solution was added to the solution, which was concentrated under reduced pressure. The resulting residue was recrystallized from methanol - ethyl

30

acetate, to give the titled compound.

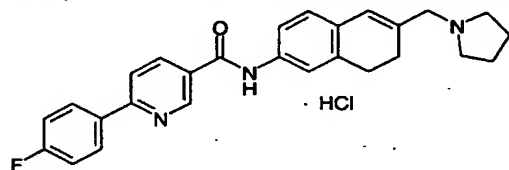
¹H-NMR (DMSO-d₆) δ: 1.43 (1H, m), 2.06 (1H, m), 2.21 (1H, m), 2.45 (1H, m), 2.79 (6H, s), 2.92 (1H, dd, J=16.2, 4.2 Hz), 3.08 (2H, d, J=6.4 Hz), 3.33 (2H, s), 7.05 (1H, d, J=8.4 Hz), 7.34 (2H, dd, J=8.9, 8.9 Hz), 7.53 (1H, d, J=8.4 Hz), 7.59 (1H, s), 7.80 (4H, m), 8.06 (2H, d, J=8.1 Hz), 10.02 (1H, s), 10.03 (1H, brs).

Melting point: 240-245 °C (crystallization solvent: methanol - ethyl acetate)

10

Example 170

6-(4-Fluorophenyl)-N-[6-(1-pyrrolidinymethyl)-7,8-dihydro-2-naphthalenyl]nicotinamide hydrochloride



15

The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(1-pyrrolidinymethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

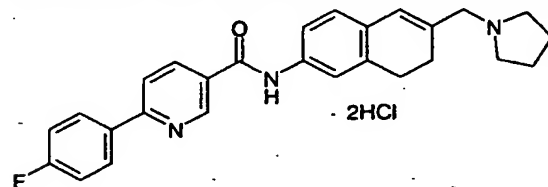
¹H-NMR (DMSO-d₆) δ: 1.70 (4H, m), 2.26 (2H, t, J=8.1 Hz), 2.44 (4H, m), 2.76 (2H, t, J=8.1 Hz), 3.12 (2H, s), 3.34 (1H, s), 6.36 (1H, s), 7.03 (1H, d, J=7.8 Hz), 7.37 (2H, dd, J=8.4, 7.0 Hz), 7.57 (1H, d, J=8.4 Hz), 7.59 (1H, s), 8.13-8.42 (4H, m), 9.19 (1H, s), 10.43 (1H, s).

Melting point: 229-231 °C (crystallization solvent: methanol - ethyl acetate)

25

Example 171

6-(4-Fluorophenyl)-N-[6-(1-pyrrolidinymethyl)-7,8-dihydro-2-naphthalenyl]nicotinamide dihydrochloride



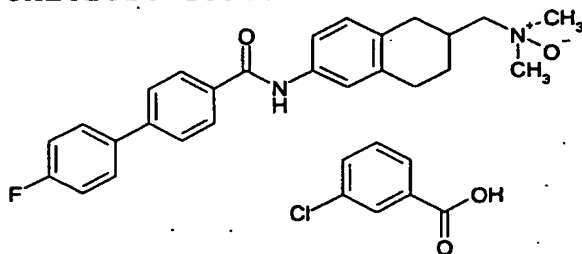
30

The titled compound was obtained by carrying out the same operation as in Example 1, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

- 5 ¹H-NMR (DMSO-d₆) δ: 2.00 (4H, m), 2.45 (4H, m), 2.83 (2H, t, J=8.1 Hz), 3.05 (2H, m), 3.47 (2H, m), 3.88 (1H, s), 6.69 (1H, s), 7.13 (1H, d, J=8.1 Hz), 7.38 (2H, dd, J=8.9, 8.6 Hz), 7.64 (1H, d, J=10.6 Hz), 7.66 (1H, s), 8.14-8.42 (4H, m), 9.19 (1H, s), 10.52 (1H, s), 10.60 (1H, brs).
- 10 Melting point: 245-248 °C (crystallization solvent: methanol - ethyl acetate)

Example 172

- 15 N-[6-[(Dimethylnitroyl)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4'-fluoro[1,1'-biphenyl]-4-carboxamide 3-chlorobenzoate

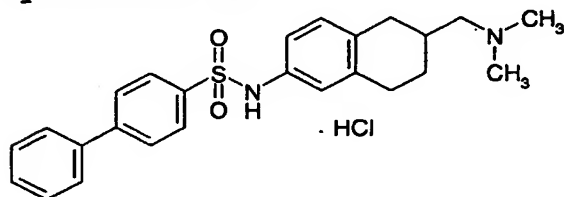


- 4'-FluoroN-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide (100 mg) obtained in Example 42 was dissolved in acetone (10 ml), which was stirred under ice-cooling.
- 20 3-Chloroperbenzoic acid (purity : 50%) (86 mg) was added to the solution, which was stirred under ice-cooling for 1 hour. The reaction mixture was concentrated under
- 25 reduced pressure, and the residue was washed with diisopropyl ether, to give the titled compound (158 mg).
- ¹H-NMR (DMSO-d₆) δ: 1.57 (1H, m), 2.07 (1H, m), 2.61 (1H, m), 2.82 (2H, m), 3.04 (1H, m), 3.33 (1H, m), 3.48 (6H, s), 3.56-3.67 (2H, m), 6.55 (1H, s), 7.03 (1H, d, J=8.4 Hz),
- 30 7.30-7.56 (6H, m), 7.78-7.85 (6H, m), 8.04 (2H, d, J=8.4 Hz), 10.17 (1H, s).

FABMS(pos) 419.1 [M+H]⁺

Example 173

5 N-[6-[(Dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-sulfonamide hydrochloride



6-[(N, N-Dimethylamino)methyl]-7,8-dihydro-2-naphthalenamine (200 mg, 0.72 mmol) obtained in Example 10 41-2) was dissolved in acetonitrile (30 ml). Triethylamine (0.401 ml, 2.88 mmol) and [1,1'-biphenyl]-4-sulfonylchloride (200 mg, 0.79 mmol) were added to the solution under ice-cooling, which was stirred for 3 hours. The reaction mixture was concentrated. Ethyl 15 acetate and water were added to the residue, and extraction was conducted. The ethyl acetate layer was concentrated, and the residue was purified by alumina column chromatography (development solvent; ethyl acetate:n-hexane = 33:67). 4N Hydrogen chloride-ethyl acetate 20 solution was added to the resulting oily substance, which was concentrated. The residue was recrystallized from methanol - ethyl acetate, to give the titled compound (194 mg).

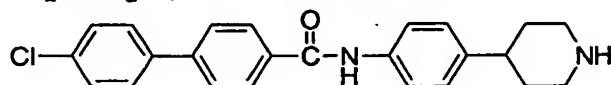
¹H-NMR (DMSO-d₆) δ: 1.32 (1H, m), 1.96 (1H, m), 2.11 (1H, 25 m), 2.35 (1H, d, J=15.9, 10.0 Hz), 2.74 (2H, m), 2.78 (7H, m), 3.02 (2H, m), 6.89 (2H, d, J=10.6 Hz), 6.91 (1H, m), 7.40-7.51 (3H, m), 7.70 (2H, d, J=6.7 Hz), 7.85 (4H, m), 9.92 (1H, brs), 10.23 (1H, s).

Melting point: 168-170 °C (crystallization solvent: 30 methanol - ethyl acetate)

FABMS(pos) 421.1 [M+H]⁺

Example 174

4'-Chloro-N-[4-(4-piperidininyl)phenyl][1,1'-biphenyl]-4-carboxamide

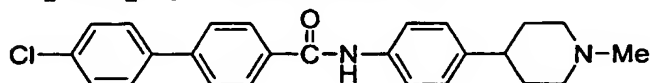


5 The titled compound was obtained as a colorless powder by carrying out the same operation as in Example 127-2), using 4'-chloro-N-[4-(4-piperidininyl)phenyl][1,1'-biphenyl]-4-carboxamide obtained in Reference Example 89. ¹H-NMR (CDCl₃+ DMSO-d₆) δ: 1.40-1.90 (4H, m), 2.60-2.90 (3H, m), 3.18-3.28 (2H, m), 7.19 (2H, d, J=8.1 Hz), 7.49 (2H, d, J=7.0 Hz), 7.67-7.75 (6H, m), 8.07-8.10 (3H, m), 10.16 (1H, s).

10 Melting point: 276-281 °C (decomposition) (crystallization solvent: ethyl acetate)

Example 175

4'-Chloro-N-[4-(1-methyl4-piperidininyl)phenyl][1,1'-biphenyl]-4-carboxamide



20 A mixture of 4'-chloro-N-[4-(4-piperidininyl)phenyl][1,1'-biphenyl]-4-carboxamide (0.17 g) obtained in Example 174, 37% aqueous formaldehyde solution (0.05 ml) and formic acid (0.5 ml) was heated at 100°C for 4 hours. The reaction mixture was cooled to room temperature. Water was added to the mixture, which was made alkaline with 8N aqueous sodium hydroxide solution, and extracted with ethyl acetate - tetrahydrofuran (1:1) mixed solution. The extract was washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and then the solvent was distilled out under reduced pressure. The resulting solid was washed with ethyl acetate, dried under reduced pressure, to give the titled compound (90 mg).

30 ¹H-NMR (CDCl₃+ DMSO-d₆) δ: 1.55-1.80 (2H, m), 1.90-2.10

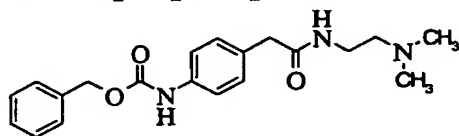
(2H, m), 2.22 (3H, s), 2.30-2.45 (1H, m), 2.80-3.20 (4H, m), 7.11 (2H, d, J=8.1 Hz), 7.36 (2H, d, J=8.1 Hz), 7.50-7.63 (6H, m), 7.97 (2H, d, J=8.4 Hz), 9.79 (1H, s).

Melting point: 273-277 °C (decomposition) (Washing

5 solvent: ethyl acetate)

Example 176

Benzyl 4-[2-[[2-(dimethylamino)ethyl]amino]-2-oxoethyl]phenylcarbamate

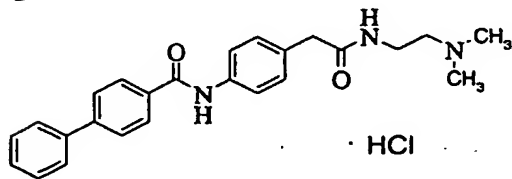


N,N-Dimethylethylenediamine (0.64 ml), WSC (1.31 g), HOBT (1.05 g), and triethylamine (2.4 ml) were added to a tetrahydrofuran (50 ml) solution of 2-[4-[[[(benzyloxy)carbonyl]amino]phenyl]acetic acid (1.5 g) obtained in Reference Example 90. After stirring for 20 hours, the reaction mixture was poured into water, and extraction was conducted using ethyl acetate. The organic layer was washed with water, saturated aqueous sodium bicarbonate solution, and saturated aqueous sodium chloride solution, dried and then concentrated. The residue was recrystallized from ethyl acetate - hexane, to give the titled compound (1.72 g).

Melting point: 126-127 °C.

25 Example 177

N-[4-[2-[[2-(Dimethylamino)ethyl]amino]-2-oxoethyl]phenyl][1,1'-biphenyl]-4-carboxamide hydrochloride



30 Oxalyl chloride (0.56 ml) was added dropwise to a

tetrahydrofuran (45 ml) solution of 4-biphenylcarboxylic acid (1.01 g) under ice-cooling. 9 drops of DMF was added to the mixture, and the temperature of the mixture was raised to room temperature, which was stirred for 40 minutes. The reaction mixture was concentrated and dried.

A tetrahydrofuran (50 ml) solution of the residue was added dropwise to a tetrahydrofuran (45 ml) solution of 2-(4-aminophenyl)-N-[2-(dimethylamino)ethyl]acetamide (939 mg) obtained in Reference Example 91 under ice-cooling.

Then the temperature of the reaction mixture was raised to room temperature, which was stirred for 2 hours.

Saturated aqueous sodium bicarbonate solution was added to the reaction mixture, and extraction was conducted using ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried over sodium sulfate, and then concentrated. The residue was dissolved in tetrahydrofuran. 4N Hydrochloric acid-ethyl acetate was added to the solution, which was concentrated.

The residue was recrystallized from methanol - diisopropyl ether, to give the titled compound (750 mg). Melting point: 216-217 °C.

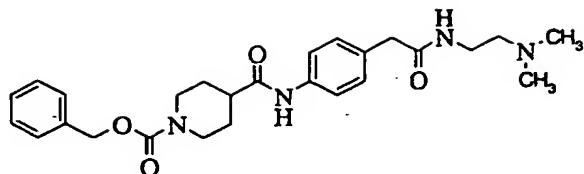
The above N-[4-[2-[[2-(dimethylamino)ethyl]amino]-2-oxoethyl]phenyl][1,1'-biphenyl]-4-carboxamide hydrochloride (100 mg) was dissolved in saturated aqueous sodium bicarbonate solution, and extraction was conducted using tetrahydrofuran-ethyl acetate (1:1). The organic layer was washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, and then concentrated.

The residue was recrystallized from methanol - diisopropyl ether, to give a free base form (56 mg) of the titled compound.

Melting point: 228-229 °C.

Example 178

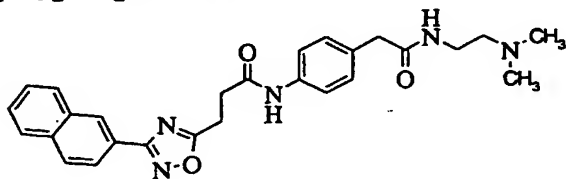
Benzyl 4-[[4-[2-[[2-(dimethylamino)ethyl]amino]-2-oxoethyl]anilino]carbonyl]-1-piperidinecarboxylate



2-(4-Aminophenyl)-N-[2-(dimethylamino)ethyl]acetamide (221 mg), WSC (249 mg), 1-hydroxybenzotriazole (199 mg), triethylamine (0.4 ml), and dimethylaminopyridine (244 mg) were added to a tetrahydrofuran (10 ml) solution of 1-[(benzyloxy)carbonyl]-4-piperidinecarboxylic acid (290 mg), which was stirred for 20 hours. The reaction mixture was poured into water, and extraction was conducted using ethyl acetate. The organic layer was washed with water, saturated aqueous sodium bicarbonate solution, and saturated aqueous sodium chloride solution, dried over sodium sulfate, and then concentrated. The residue was recrystallized from methanol - diisopropyl ether, to give the titled compound (230 mg). Melting point: 169-170 °C.

Example 179

N-[4-[2-[[2-(Dimethylamino)ethyl]amino]-2-oxoethyl]phenyl]-3-[3-(2-naphthyl)-1,2,4-oxadiazol-5-yl]propanamide

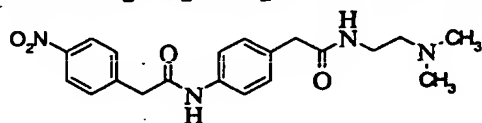


2-(4-Aminophenyl)-N-[2-(dimethylamino)ethyl]acetamide (221 mg), WSC (249 mg), 1-hydroxybenzotriazole (199 mg), triethylamine (0.4 ml), and dimethylaminopyridine (244 mg) were added to a DMF (5 ml) solution of 3-[3-(2-naphthyl)-1,2,4-oxadiazol-5-yl]propionic acid (268 mg), which was stirred for 5 hours. The reaction mixture was poured into water, and extraction was conducted using ethyl acetate. The organic layer was

washed with water, saturated aqueous sodium bicarbonate solution, and saturated aqueous sodium chloride solution, dried over sodium sulfate, and then concentrated. The residue was recrystallized from methanol, to give the
5 titled compound (166 mg).
Melting point: 173-174 °C.

Example 180

N-[4-[2-[[2-(Dimethylamino)ethyl]amino]-2-
10 oxoethyl]phenyl]-2-(4-nitrophenyl)acetamide

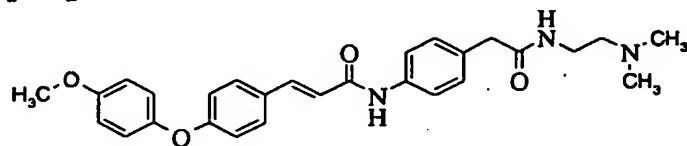


2-(4-Aminophenyl)-N-[2-
(dimethylamino)ethyl]acetamide (221 mg), WSC (free form :
0.23 ml), 1-hydroxybenzotriazole (199 mg), and
15 dimethylaminopyridine (244 mg) were added to a DMF (5 ml)
solution of 4-nitrophenylacetic acid (181 mg), which was
stirred for 4 hours. The reaction mixture was poured into
water, and extraction was conducted using ethyl acetate.
The organic layer was washed with water, saturated aqueous
20 sodium bicarbonate solution, and saturated aqueous sodium
chloride solution, dried over sodium sulfate, and then
concentrated. The residue was recrystallized from
methanol, to give the titled compound (80 mg).
Melting point: 160-162 °C.

25

Example 181

(E)-N-[4-[2-[[2-(Dimethylamino)ethyl]amino]-2-
oxoethyl]phenyl]-3-[4-(4-methoxyphenoxy)phenyl]-2-
propanamide



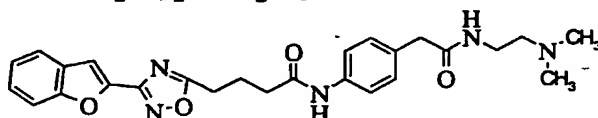
30

2-(4-Aminophenyl)-N-[2-
(dimethylamino)ethyl]acetamide (221 mg), WSC (free form :

0.23 ml), 1-hydroxybenzotriazole (199 mg), triethylamine (0.14 ml) and dimethylaminopyridine (122 mg) were added to a DMF (5 ml) solution of (E)-3-[4-(4-methoxyphenoxy)phenyl]-2-propenoic acid (270 mg), which
5 was stirred for 24 hours. The reaction mixture was poured into water, and extraction was conducted using ethyl acetate - tetrahydrofuran (1:1). The organic layer was washed with water, saturated aqueous sodium bicarbonate solution, and saturated aqueous sodium chloride solution,
10 dried over sodium sulfate, and then concentrated. The resulting crude crystals were washed with diisopropyl ether, to give the titled compound (227 mg).
Melting point: 175-177 °C (decomposition).

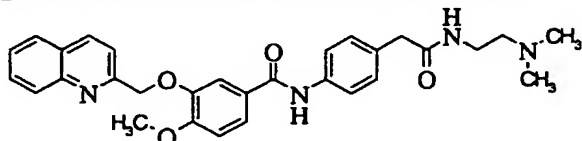
15 Compounds described in the following Example 182 to 198 were produced in the same manner as in Example 181.
Example 182

4-[3-(1-Benzofuran-2-yl)-1,2,4-oxadiazol-5-yl]-N-[4-[2-
20 [[2-(dimethylamino)ethyl]amino]-2-oxoethyl]phenyl]butanamide



Melting point: 161-163 °C.
Washing solvent: diisopropyl ether.

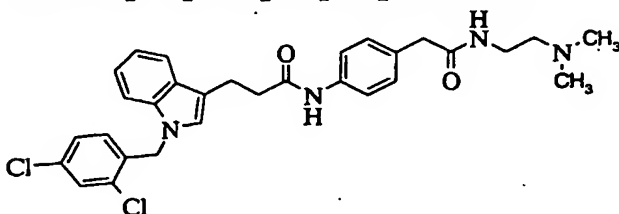
25 Example 183
N-[4-[2-[[2-(Dimethylamino)ethyl]amino]-2-oxoethyl]phenyl]-3-methoxy-4-(2-quinolinylmethoxy)benzamide



30 Melting point: 209-210 °C (decomposition).
Washing solvent: diisopropyl ether.

Example 184

3-[1-(2,4-Dichlorobenzyl)-1H-indol-3-yl]-N-[4-[2-[[2-(dimethylamino)ethyl]amino]-2-oxoethyl]phenyl]propanamide



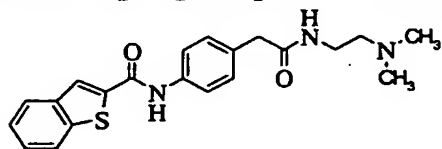
5

Melting point: : 123-125 °C (decomposition).

Washing solvent: diisopropyl ether.

Example 185

10 N-[4-[2-[[2-(Dimethylamino)ethyl]amino]-2-oxoethyl]phenyl]-1-benzothiophen-2-carboxamide



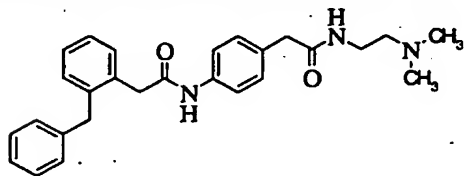
Melting point: 186-187 °C (decomposition).

Washing solvent: diisopropyl ether.

15

Example 186

2-(2-Benzylphenyl)-N-[4-[2-[[2-(dimethylamino)ethyl]amino]-2-oxoethyl]phenyl]acetamide

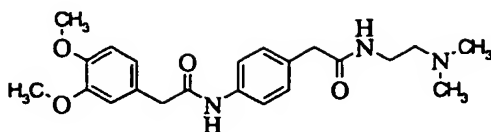


20 Melting point: 115-117 °C.

Washing solvent: diisopropyl ether.

Example 187

25 2-(3,4-dimethoxyphenyl)-N-[4-[2-[[2-(dimethylamino)ethyl]amino]-2-oxoethyl]phenyl]acetamide

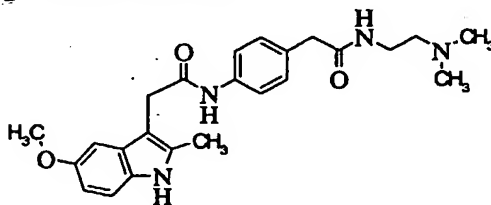


Melting point: 123-124 °C.

Recrystallization solvent: methanol - diisopropyl ether.

5 Example 188

N-[4-[2-[[2-(Dimethylamino)ethyl]amino]-2-oxoethyl]phenyl]-2-(5-methoxy-2-methyl-1H-indol-3-yl)acetamide

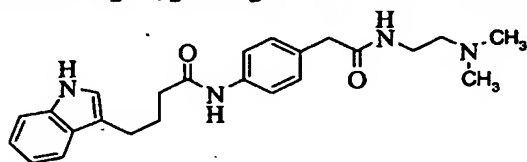


10 Melting point: 125-126 °C.

Recrystallization solvent: methanol - diisopropyl ether.

Example 189

15 N-[4-[2-[[2-(Dimethylamino)ethyl]amino]-2-oxoethyl]phenyl]-4-(1H-indol-3-yl)butanamide

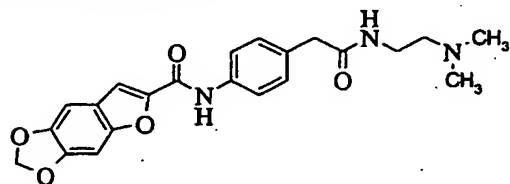


Melting point: 132-133 °C.

Washing solvent: diisopropyl ether.

20 Example 190

N-[4-[2-[[2-(Dimethylamino)ethyl]amino]-2-oxoethyl]phenyl]furo[2,3-f][1,3]benzodioxol-6-carboxamide

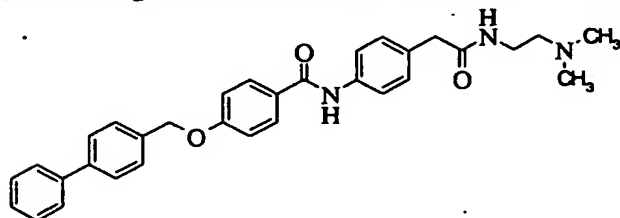


Melting point: : 173-175 °C (decomposition).

Washing solvent: diisopropyl ether.

Example 191

- 5 4-([1,1'-Biphenyl]-4-ylmethoxy)-N-[4-[2-[[2-(dimethylamino)ethyl]amino]-2-oxoethyl]phenyl]benzamide



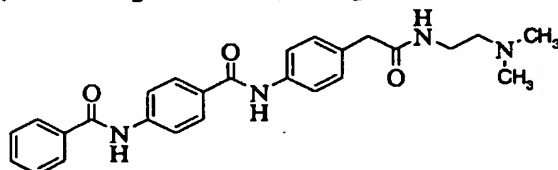
Melting point: 204-208 °C.

Washing solvent: diisopropyl ether.

10

Example 192

- 4-(Benzoylamino)-N-[4-[2-[[2-(dimethylamino)ethyl]amino]-2-oxoethyl]phenyl]benzamide

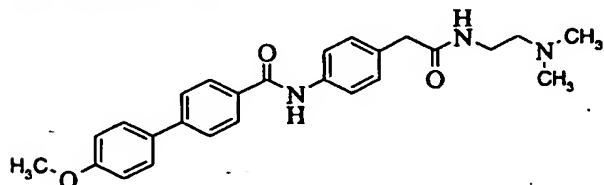


- 15 Melting point: 220-221 °C.

Washing solvent: diisopropyl ether.

Example 193

- 20 N-[4-[2-[[2-(Dimethylamino)ethyl]amino]-2-oxoethyl]phenyl]-4'-methoxy[1,1'-biphenyl]-4-carboxamide



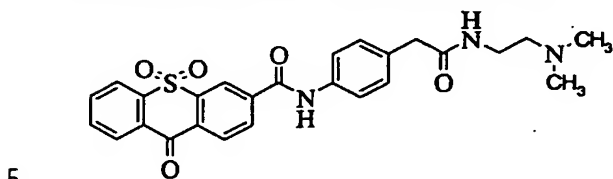
Melting point: 196-198 °C (decomposition).

Washing solvent: diisopropyl ether.

25

Example 194

N-[4-[2-[[2-(Dimethylamino)ethyl]amino]-2-oxoethyl]phenyl]-9,10,10-trioxo-9,10-dihydro-10 λ^6 -thioxanten-3-carboxamide

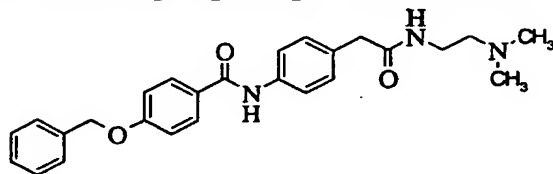


Melting point: : 162-163 °C (decomposition).

Washing solvent: diisopropyl ether.

Example 195

10 4-(Benzyloxy)-N-[4-[2-[[2-(dimethylamino)ethyl]amino]-2-oxoethyl]phenyl]benzamide

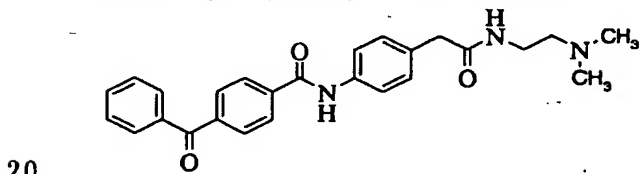


Melting point: 190-192 °C (decomposition).

15 Washing solvent: diisopropyl ether.

Example 196

4-Benzoyl-N-[4-[2-[[2-(dimethylamino)ethyl]amino]-2-oxoethyl]phenyl]benzamide

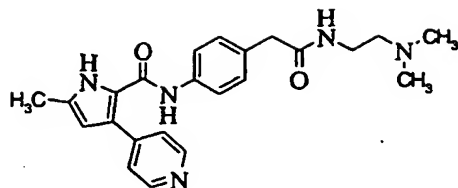


Melting point: 173-175 °C (decomposition).

Washing solvent: diisopropyl ether.

Example 197

25 N-[4-[2-[[2-(Dimethylamino)ethyl]amino]-2-oxoethyl]phenyl]-5-methyl-3-(4-pyridinyl)-1H-pyrrole-2-carboxamide

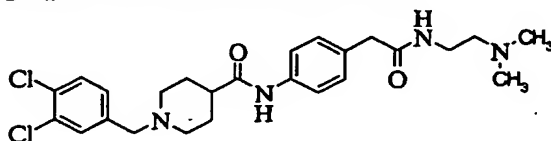


Melting point: : 215-218 °C (decomposition).

Washing solvent: diisopropyl ether.

5 Example 198

1-(3,4-Dichlorobenzyl)-N-[4-[2-[[2-(dimethylamino)ethyl]amino]-2-oxoethyl]phenyl]-4-piperidinecarboxamide

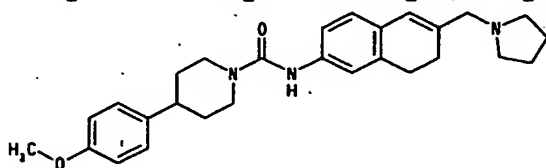


10 Melting point: : 182-183 °C (decomposition).

Washing solvent: diisopropyl ether.

Example 199

4-(4-Methoxyphenyl)-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide



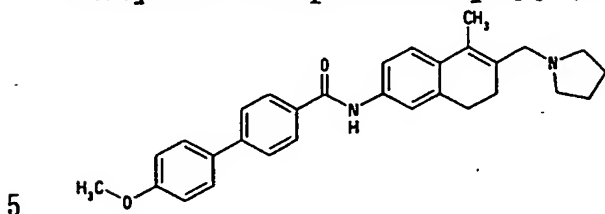
The titled compound was obtained by carrying out the same operation as in Example 99, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

¹H-NMR (CDCl₃) δ: 1.61-1.91 (8H, m), 2.31 (2H, t, J=8.1 Hz), 2.54 (4H, m), 2.73-2.81 (3H, m), 2.98 (2H, t, J=7.8 Hz), 3.16 (2H, s), 3.79 (3H, s), 4.20 (2H, d, J=13.1 Hz), 6.31 (1H, s), 6.36 (1H, s), 6.86 (2H, d, J=8.6 Hz), 7.06-7.20 (5H, m).

Melting point: 175-176 °C (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 200

4'-Methoxy-N-[6-(1-pyrrolidinymethyl)-5-methyl-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 5-methyl-6-(1-pyrrolidinymethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 69.

10 $^1\text{H-NMR}$ (CDCl_3) δ : 1.78 (4H, m), 2.10 (3H, s), 2.37 (2H, t, $J=8.1$ Hz), 2.53 (4H, m), 2.76 (2H, t, $J=8.1$ Hz), 3.28 (2H, s), 3.87 (3H, s), 7.01 (2H, d, $J=8.6$ Hz), 7.27 (1H, d, $J=7.8$ Hz), 7.46 (1H, d, $J=7.8$ Hz), 7.48 (1H, s), 7.57 (2H, d, $J=8.6$ Hz), 7.66 (2H, d, $J=8.4$ Hz), 7.81 (1H, s), 7.92 (2H, d, $J=8.4$ Hz).

15 Elemental analysis for $\text{C}_{30}\text{H}_{32}\text{N}_2\text{O}_2$

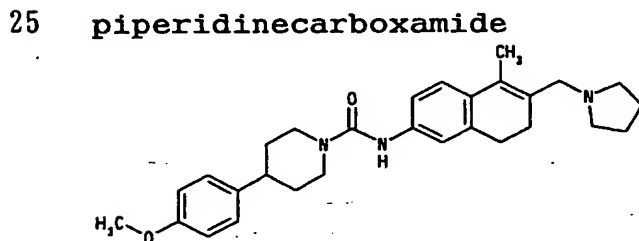
Calcd.: C, 79.61; H, 7.13; N, 6.19

Found: C, 79.35; H, 7.28; N, 6.24

Melting point: 179-180 $^{\circ}\text{C}$ (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 201

4-(4-Methoxyphenyl)-N-[6-(1-pyrrolidinymethyl)-5-methyl-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide



The titled compound was obtained by carrying out the same operation as in Example 99, using 5-methyl-6-(1-pyrrolidinymethyl)-7,8-dihydro-2-naphthalenamine

obtained in Reference Example 69.

¹H-NMR (CDCl₃) δ: 1.67 (2H, dd, J=13.4, 4.0 Hz), 1.78 (4H, m), 1.89 (2H, d, J=11.4 Hz), 2.07 (3H, s), 2.34 (2H, t, J=7.5 Hz), 2.52 (4H, m), 2.68-2.73 (3H, m), 2.98 (2H, t, J=7.5 Hz), 3.26 (2H, s), 3.80 (3H, s), 4.20 (2H, d, J=13.4 Hz), 6.36 (1H, s), 6.86 (2H, d, J=8.4 Hz), 7.12-7.20 (5H, m).

Elemental analysis for C₂₈H₃₇N₃O₂

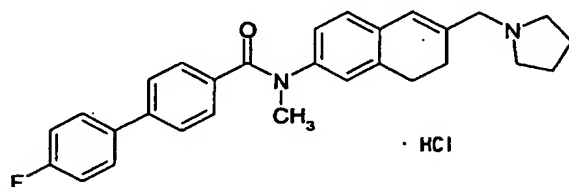
Calcd.: C, 75.13; H, 8.33; N, 9.39

Found: C, 74.96; H, 8.14; N, 9.10

Melting point: 163-164 °C (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 202

4'-Fluoro-N-methyl-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide hydrochloride



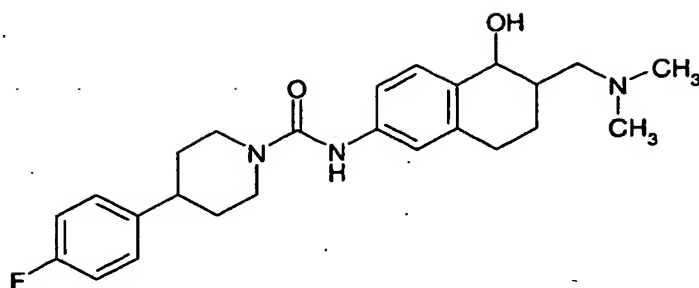
The titled compound was obtained by carrying out the same operation as in Example 1, using N-methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine hydrochloride obtained in Reference Example 95.

¹H-NMR (DMSO-d₆) δ: 1.92-1.98 (4H, m), 2.39 (2H, t, J=8.1 Hz), 2.73 (2H, t, J=8.1 Hz), 3.00 (2H, m), 3.35 (3H, m), 3.44 (2H, m), 3.83 (2H, d, J=5.6 Hz), 6.62 (1H, s), 6.92-7.01 (2H, m), 7.11 (1H, s), 7.26 (2H, dd, J=8.9, 5.6 Hz), 7.38 (2H, d, J=8.1 Hz), 7.55 (2H, d, J=8.1 Hz), 7.69 (2H, dd, J=8.9, 5.6 Hz), 10.60 (1H, brs).

FABMS(pos) 441.2 [M+H]⁺

Example 203

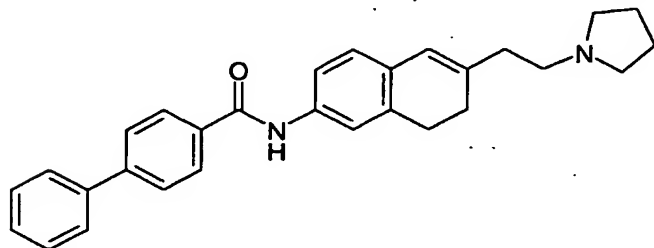
N-[6-[(Dimethylamino)methyl]-5-hydroxy-5,6,7,8-tetrahydro-2-naphthalenyl]-4-(4-fluorophenyl)-1-piperidinecarboxamide



N, N-Dimethylmethylen ammonium chloride (638 mg, 6.82 mmol) was added to a mixed solution of 4-(4-fluorophenyl)-N-(5-oxo-5,6,7,8-tetrahydro-2-naphthalenyl)-1-piperidinecarboxamide (1.00 g, 2.73 mmol) obtained in Reference Example 97 in tetrahydrofuran (10 ml) and acetonitrile (10 ml), which was stirred at room temperature for 1 day. The solvent was distilled out under reduced pressure. Ethyl acetate was added to the residue, which was washed with aqueous potassium carbonate solution and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The resulting oily substance was dissolved in methanol (15 ml). Sodium borohydride (103 mg, 2.73 mmol) was added to the solution under ice-cooling, which was stirred for 1 hour. Then, the solvent was distilled out under reduced pressure. 1N Hydrochloric acid was added to the residue, which was washed with ethyl acetate. 4N Sodium hydroxide was added to the water layer to make it alkaline. The reaction mixture was extracted with ethyl acetate, which was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The resulting residue was purified by aluminum B column chromatography (development solvent; ethyl acetate), powdered with hexane, to give the titled compound (231 mg).
Melting point: 160-163 °C (crystallization solvent: ethyl acetate - n-hexane)
FAB(pos) 426.3 [M+H]⁺

Example 204

N-[6-[2-(1-Pyrrolidinyl)ethyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



- 5 Concentrated hydrochloric acid (2 ml) was added to
N-[6-[2-(1-pyrrolidinyl)ethyl]-7,8-dihydro-2-
naphthalenyl]acetamide (98.0 mg, 0.345 mmol) obtained in
Reference Example 103, which was stirred at 100 °C for 16
hours. The solvent was distilled out under reduced
10 pressure. Ethyl acetate was added to the residue, which
was washed with aqueous potassium carbonate solution and
saturated aqueous sodium chloride solution, dried over
anhydrous sodium sulfate, and then the solvent was
distilled out under reduced pressure. WSC (62.5 mg, 0.326
15 mmol) was added to a dimethylformamide solution (1.5ml) of
the resulting oily substance (79.0 mg, 0.326 mmol),
[1,1'-biphenyl]-4-carboxylic acid (64.6 mg, 0.326 mmol)
and DMAP (39.8 mg, 0.326 mmol) under ice-cooling, which was
stirred at room temperature for 1 day. Ethyl acetate was
20 added to the reaction mixture, washed with aqueous
potassium carbonate solution and saturated aqueous sodium
chloride solution, dried over anhydrous sodium sulfate,
then the solvent was distilled out under reduced pressure.
The resulting residue was purified by aluminum column
25 chromatography (development solvent; ethyl acetate),
powdered with ethyl acetate and isopropyl ether (1:5), to
give the titled compound (36.8 mg).
¹H NMR (DMSO-d₆) δ: 1.67 (4H, m), 2.23 (2H, m), 2.34 (2H,
m), 2.46 (4H, m), 2.57 (2H, m), 2.75 (2H, m), 6.24 (1H, s),
30 6.98 (1H, d, J = 8.1 Hz), 7.40-7.59 (5H, m), 7.76 (2H, d,
J = 7.5 Hz), 7.82 (2H, d, J=8.4 Hz), 8.05 (2H, d, J = 8.4

Hz), 10.19 (1H, s).

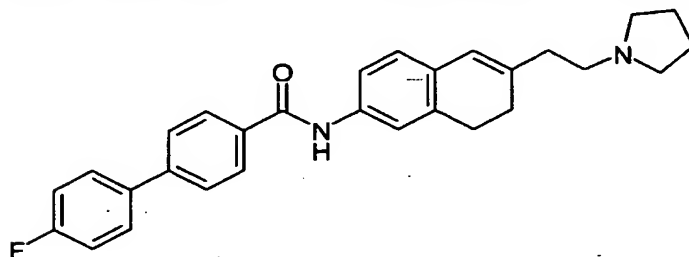
Melting point: 184-186 °C (crystallization solvent: ethyl acetate - isopropyl ether)

FAB(pos). 423.2 [M+H]⁺

5

Example 205

4'-Fluoro-N-[6-[2-(1-pyrrolidinyl)ethyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



- 10 Concentrated hydrochloric acid (2 ml) was added to N-[6-[2-(1-pyrrolidinyl)ethyl]-7,8-dihydro-2-naphthalenyl]acetamide (98.0 mg, 0.345 mmol) obtained in Reference Example 103, which was stirred at 100°C for 16 hours. The solvent was distilled out under reduced
- 15 pressure. Ethyl acetate was added to the residue, which was washed with aqueous potassium carbonate solution and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. WSC (62.5 mg, 0.326
- 20 mmol) was added to a dimethylformamide solution (1.5 ml) of the resulting oily substance (79.0 mg, 0.326 mmol), 4'-fluoro-[1,1'-biphenyl]-4-carboxylic acid (64.6 mg, 0.326 mmol) and DMAP (39.8 mg, 0.326 mmol) under ice-cooling, which was stirred at room temperature for 1 day.
- 25 Ethyl acetate was added to the reaction mixture, which was washed with aqueous potassium carbonate solution and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and the solvent was distilled out under reduced pressure. The resulting residue was
- 30 purified by aluminum column chromatography (development solvent; ethyl acetate), powdered with ethyl acetate -

isopropyl ether (1:5) , to give the titled compound (75.1 mg).

¹H NMR (DMSO-d₆) δ: 1.68 (4H, m), 2.23 (2H, m), 2.35 (2H, m), 2.50 (4H, m), 2.59 (2H, m), 2.75 (2H, m), 6.24 (1H, s),
5 6.98 (1H, d, J = 8.1 Hz), 7.34 (2H, m), 7.56 (2H, m), 7.81 (4H, m), 8.04 (2H, d, J = 8.4 Hz), 10.19 (1H, s).

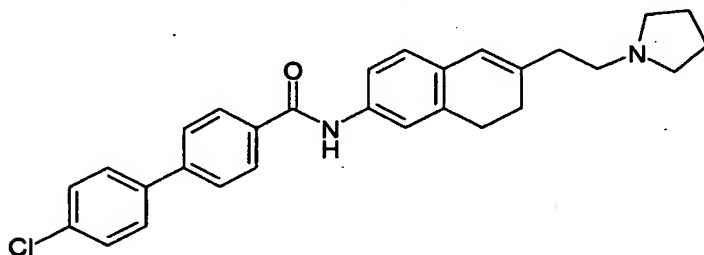
Melting point: 187-189°C (crystallization solvent: ethyl acetate - isopropyl ether)

FAB (pos) 441.3 [M+H]⁺

10

Example 206

4'-Chloro-N-[6-[2-(1-pyrrolidinyl)ethyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



15

Concentrated hydrochloric acid (2 ml) was added to N-[6-[2-(1-pyrrolidinyl)ethyl]-7,8-dihydro-2-naphthalenyl]acetamide (98.0 mg, 0.345 mmol) obtained in Reference Example 103, which was stirred at 100°C for 16 hours. The solvent was distilled out under reduced
20 pressure. Ethyl acetate was added to the residue, which was washed with aqueous potassium carbonate solution and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. WSC (62.5 mg, 0.326
25 mmol) was added to a dimethylformamide solution (1.5 ml) of the resulting oily substance (79.0 mg, 0.326 mmol), 4'-chloro-[1,1'-biphenyl]-4-carboxylic acid (64.6 mg, 0.326 mmol) and DMAP (39.8 mg, 0.326 mmol) under ice-cooling, which was stirred at room temperature for 1 day.

30

Ethyl acetate was added to the reaction mixture, which was washed with aqueous potassium carbonate solution and

saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The resulting residue was purified by aluminum column chromatography (development solvent; ethyl acetate), powdered with ethyl acetate - isopropyl ether (1:5), to give the titled compound (78.4 mg).

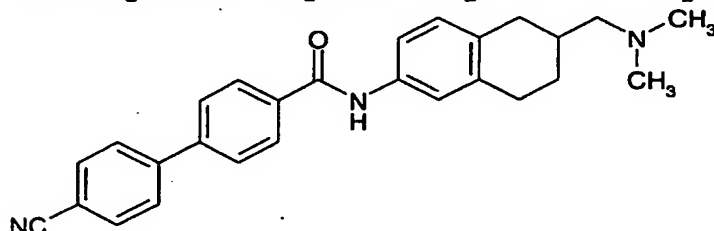
¹H NMR (DMSO-d₆) δ: 1.67 (4H, m), 2.23 (2H, m), 2.34 (2H, m), 2.45 (4H, m), 2.57 (2H, m), 2.75 (2H, m), 6.24 (1H, s), 6.98 (1H, d, J = 8.1 Hz), 7.55 (4H, m), 7.80 (2H, d, J=8.4 Hz), 7.84 (2H, d, J=8.4 Hz), 8.05 (2H, d, J = 8.7 Hz), 10.20 (1H, s).

Melting point: 207-209°C (crystallization solvent: ethyl acetate - isopropyl ether)

FAB (pos) 457.2 [M+H]⁺

Example 207

4'-Cyano-N-[6-[(dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using N-[(6-amino-1,2,3,4-tetrahydro-2-naphthalenyl)methyl]-N,N-dimethylamine and 4'-cyano-[1,1'-biphenyl]-4-carboxylic acid.

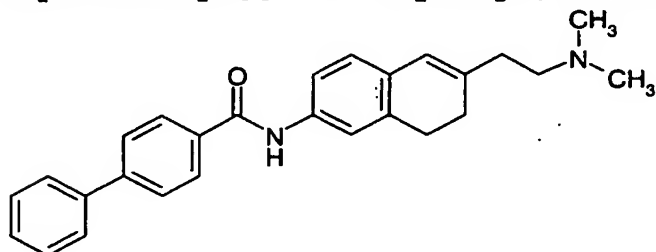
¹H NMR (CDCl₃) δ: 1.42 (1H, m), 1.95 (2H, m), 2.26 (6H, s), 2.24-2.46 (3H, m), 2.84-2.95 (3H, m), 7.10 (1H, d, J=8.4 Hz), 7.30 (1H, m), 7.46 (1H, s), 7.74 (7H, m), 7.98 (2H, d, J=8.4 Hz).

Melting point: 183-185°C (crystallization solvent: ethyl acetate - isopropyl ether)

FAB (pos) 410.2 [M+H]⁺

Example 208

N-[6-[2-(Dimethylamino)ethyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



5

Concentrated hydrochloric acid (1.5 ml) was added to N-[6-[2-(dimethylamino)ethyl]-7,8-dihydro-2-naphthalenyl]acetamide (57.5 mg, 0.223 mmol) obtained in Reference Example 104, which was stirred at 100°C for 1
10 hour. The solvent was distilled out under reduced pressure. Ethyl acetate was added to the residue, which was washed with aqueous potassium carbonate solution and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was
15 distilled out under reduced pressure. WSC (29.2 mg, 0.139 mmol) was added to a dimethylformamide solution (0.7 ml) of the resulting oily substance (30 mg, 0.139 mmol), [1,1'-biphenyl]-4-carboxylic acid (30.2 mg, 0.139 mmol) and DMAP (16.9 mg, 0.139 mmol) under ice-cooling, which was
20 stirred at room temperature for 16 hours. Ethyl acetate was added to the reaction mixture, which was washed with aqueous potassium carbonate solution and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under
25 reduced pressure. The resulting residue was purified by aluminum column chromatography (development solvent; ethyl acetate), powdered with ethyl acetate - isopropyl ether (1:5), to give the titled compound (12.4 mg).
¹H NMR (CDCl₃) δ: 2.29 (8H, m), 2.41 (2H, m), 2.46 (2H, m),
30 2.84 (2H, t, J = 8.1 Hz), 6.24 (1H, s), 6.98 (1H, d, J = 8.4 Hz), 7.34 (1H, m), 7.41 (1H, d, J = 6.9 Hz), 7.46 (3H,

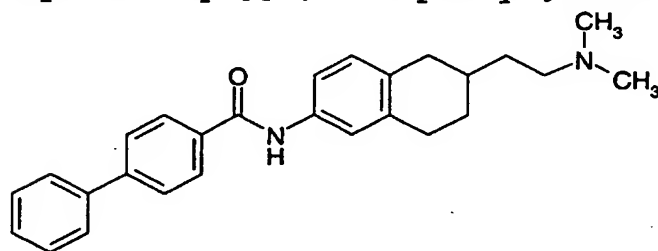
m), 7.63 (2H, d, J = 7.2 Hz), 7.71 (2H, d, J = 8.4 Hz), 7.77 (1H, br), 7.94 (2H, d, J = 8.4 Hz).

Melting point: 148-150°C (crystallization solvent: ethyl acetate - isopropyl ether)

5 FAB (pos) 397.2 [M+H]⁺

Example 209

N-[6-[2-(Dimethylamino)ethyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



10

A methanol solution (5 ml) of N-[6-[2-(dimethylamino)ethyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide (20 mg, 0.050 mmol) obtained in Example 208 and palladium carbon (10 mg) was stirred under hydrogen atmosphere for 4 hours. After a catalyst was filtered off, the filtrate was concentrated under reduced pressure. The resulting residue was purified by aluminum B column chromatography (development solvent; ethyl acetate), powdered with ethyl acetate - hexane (1:3), to give the titled compound (4.0 mg).

15

¹H NMR (CDCl₃) δ: 1.60 (4H, m), 1.92 (1H, m), 2.26 (6H, s), 2.42 (3H, m), 2.84 (3H, m), 7.06 (1H, d, J=8.1Hz), 7.32 (1H, m), 7.46 (4H, m), 7.63 (2H, d, J=6.9Hz), 7.72 (3H, m), 7.94 (2H, d, J=8.1Hz).

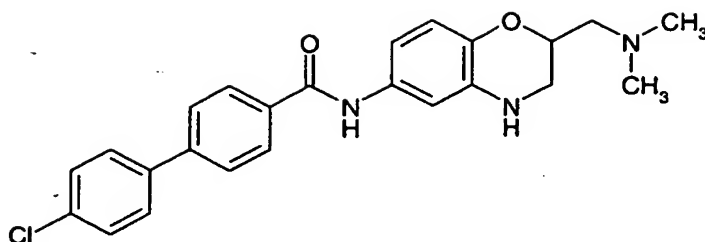
20

25 Melting point: 112-114°C (crystallization solvent: ethyl acetate - isopropyl ether)

FAB(pos) 399.2 [M+H]⁺

Example 210

30 4'-Chloro-N-[2-[(dimethylamino)methyl]-3,4-dihydro-2H-1,4-benzoxazin-6-yl][1,1'-biphenyl]-4-carboxamide



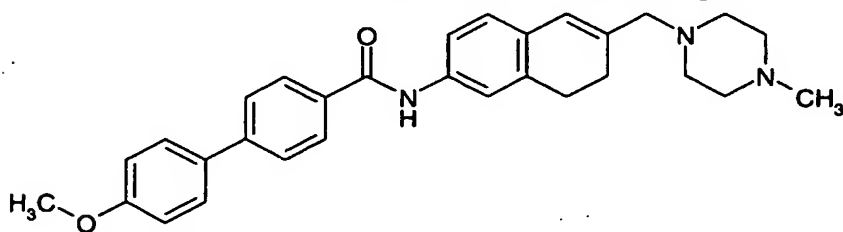
The titled compound was obtained as white powders by the same method as in Example 1, using 6-amino-2-(dimethylamino)methyl-1,4-benzoxazin obtained in Reference Example 105.

¹H-NMR (CDCl₃) δ: 2.33 (6H, s), 2.44-2.65 (2H, m), 3.15-3.21 (1H, m), 3.41-3.46 (1H, m), 3.87 (1H, brs), 4.24-4.26 (1H, m), 6.61 (1H, dd, J=2.5, 8.6 Hz), 6.81 (1H, d, J=8.6 Hz), 7.28 (1H, d, J=2.5 Hz), 7.43 (2H, d, J=6.5 Hz), 7.54 (2H, d, J=6.5 Hz), 7.64 (2H, d, J=8.4 Hz), 7.71 (1H, s), 7.90 (2H, d, J=8.4 Hz).

Melting point: 227-230 °C (crystallization solvent: diisopropyl ether)

Example 211

4'-Methoxy-N-[6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



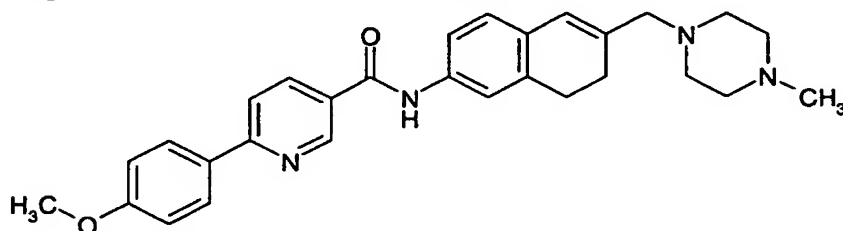
The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using 6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 106.

¹H NMR (CDCl₃) δ: 2.31 (3H, s), 2.33 (2H, t, J=8.1 Hz), 2.49 (8H, bs), 2.84 (2H, t, J=8.1 Hz), 3.07 (2H, s), 3.87 (3H, s), 6.36 (1H, s), 7.00-7.03 (3H, m), 7.36 (1H, d, J=8.1 Hz), 7.51 (1H, s), 7.58 (2H, d, J=8.4 Hz), 7.67 (2H, d, J=8.4 Hz), 7.78 (1H, s), 7.91 (2H, d, J=8.4 Hz).

Melting point: 208-210 °C (crystallization solvent: ethyl acetate)

Example 212

- 5 6-(4-Methoxyphenyl)-N-[6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl]nicotinamide



- 10 The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using 6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 106.

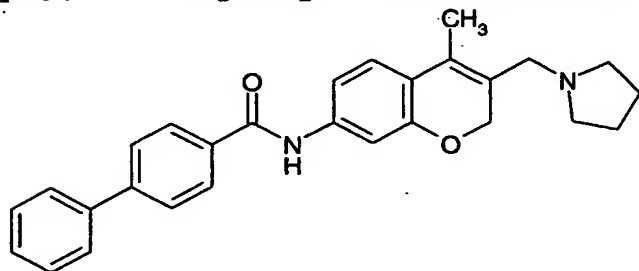
- 15 ¹H NMR (CDCl₃) δ: 2.30 (3H, s), 2.33 (2H, t, J=8.1 Hz), 2.47 (8H, bs), 2.84 (2H, t, J=8.1 Hz), 3.07 (2H, s), 3.89 (3H, s), 6.36 (1H, s), 7.01-7.04 (3H, m), 7.37 (1H, d, J=8.1 Hz), 7.49 (1H, s), 7.78-7.81 (2H, m), 8.03 (2H, d, J=8.4 Hz), 8.21 (1H, dd, J=2.1 Hz, 8.7 Hz), 9.09 (1H, s).

Melting point: 235-237 °C (crystallization solvent: ethyl acetate)

20

Example 213

- N-[4-Methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-yl][1,1'-biphenyl]-4-carboxamide



25

The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using

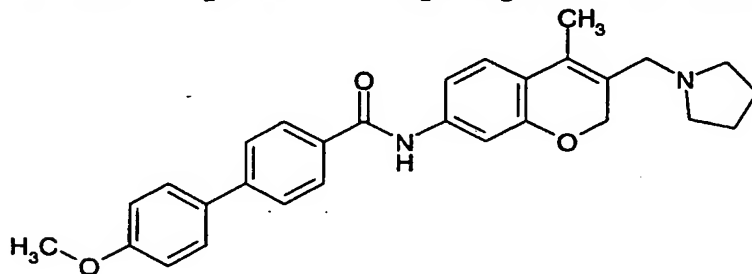
4-methyl-3-(1-pyrrolidinymethyl)-2H-chromen-7-amine
obtained in Reference Example 107.

¹H NMR (CDCl₃) δ: 1.77 (4H, s), 2.05 (3H, s), 2.51 (4H, s),
3.25 (2H, s), 4.74 (2H, s), 7.14-7.50 (6H, m), 7.63 (2H,
5 d, J=7.2 Hz), 7.71 (2H, d, J=8.4 Hz), 7.79 (1H, s), 7.94
(2H, d, J=8.4 Hz).

Melting point: 176-178 °C (crystallization solvent:
ethyl acetate - diisopropyl ether)

10 Example 214

4'-Methoxy-N-[4-methyl-3-(1-pyrrolidinymethyl)-2H-
chromen-7-yl][1,1'-biphenyl]-4-carboxamide



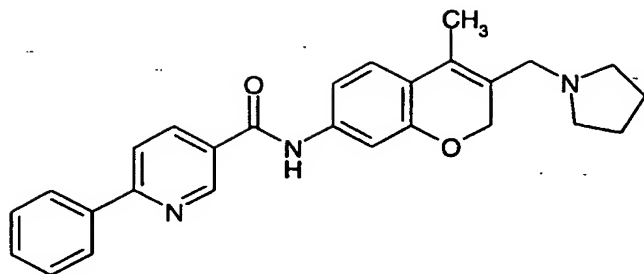
The titled compound was obtained as colorless powders
15 by carrying out the same operation as in Example 1, using
4-methyl-3-(1-pyrrolidinymethyl)-2H-chromen-7-amine
obtained in Reference Example 107.

¹H NMR (CDCl₃) δ: 1.77 (4H, s), 2.05 (3H, s), 2.51 (4H, s),
3.25 (2H, s), 3.87 (3H, s), 4.74 (2H, s), 7.01 (2H, d, J=8.7
20 Hz), 7.14-7.31 (3H, m), 7.57 (2H, d, J=8.7 Hz), 7.66 (2H,
d, J=8.4 Hz), 7.89 (1H, s), 7.91 (2H, d, J=8.4 Hz).

Melting point: 195-197 °C (crystallization solvent:
ethyl acetate - diisopropyl ether)

25 Example 215

N-[4-Methyl-3-(1-pyrrolidinymethyl)-2H-chromen-7-yl]-
6-phenylnicotinamide



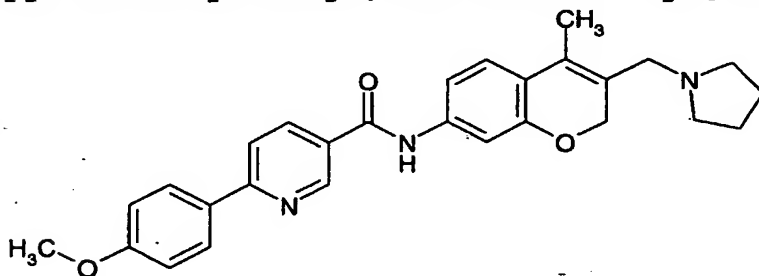
The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using 4-methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-amine
5 obtained in Reference Example 107.

^1H NMR (CDCl_3) δ : 1.77 (4H, s), 2.05 (3H, s), 2.51 (4H, s), 3.25 (2H, s), 4.74 (2H, s), 7.14-7.28 (3H, m), 7.47-7.54 (3H, m), 7.81-7.87 (2H, m), 8.06 (2H, d, $J=8.4$ Hz), 8.27 (1H, d, $J=8.4$ Hz), 9.13 (1H, s).

10 Meltingpoint: 192-193 $^{\circ}\text{C}$ (crystallization solvent: ethyl acetate)

Example 216

6-(4-Methoxyphenyl)-N-[4-methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-yl]nicotinamide
15



The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using 4-methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-amine
20 obtained in Reference Example 107.

^1H NMR (CDCl_3) δ : 1.77 (4H, s), 2.05 (3H, s), 2.51 (4H, s), 3.25 (2H, s), 3.89 (3H, s), 4.74 (2H, s), 7.03 (2H, d, $J=8.7$ Hz), 7.14-7.26 (3H, m), 7.75-7.81 (2H, m), 8.03 (2H, d, $J=8.7$ Hz), 8.21 (1H, d, $J=6.6$ Hz), 9.09 (1H, s).

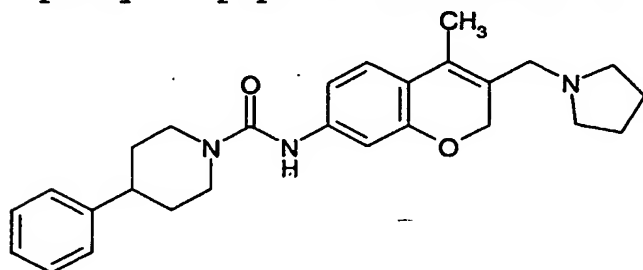
25 Meltingpoint: 201-203 $^{\circ}\text{C}$ (crystallization solvent: ethyl

acetate)

Example 217

N-[4-Methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-yl]-

5 4-phenyl-1-piperidinecarboxamide



The titled compound was obtained as colorless powders by carrying out the same operation as in Example 99, using 4-methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-amine obtained in Reference Example 107.

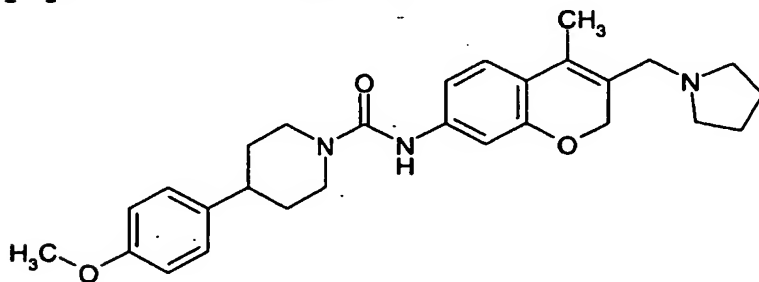
^1H NMR (CDCl_3) δ : 1.72-1.95 (8H, m), 2.03 (3H, s), 2.54 (4H, s), 2.63-2.76 (1H, m), 2.95-3.00 (2H, m), 3.27 (2H, s), 4.19-4.23 (2H, m), 4.70 (2H, s), 6.39 (1H, s), 6.83 (1H, s), 7.01-7.32 (7H, m).

15 Melting point: 125-127 °C (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 218

4-(4-Methoxyphenyl)-N-[4-methyl-3-(1-

20 pyrrolidinylmethyl)-2H-chromen-7-yl]-1-piperidinecarboxamide



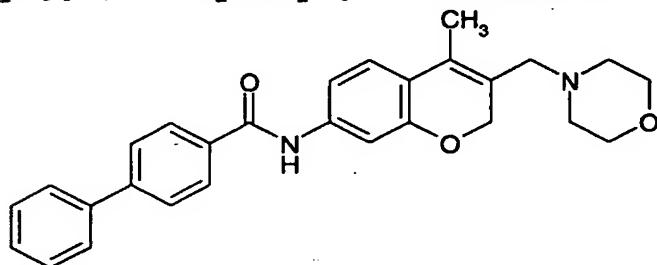
The titled compound was obtained as colorless powders by carrying out the same operation as in Example 99, using 4-methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-amine

obtained in Reference Example 107.

¹H NMR (CDCl₃) δ: 1.63-1.91 (8H, m), 2.02 (3H, s), 2.49 (4H, s), 2.61-2.71 (1H, m), 2.93-3.01 (2H, m), 3.23 (2H, s), 3.79 (3H, s), 4.16-4.21 (2H, m), 4.69 (2H, s), 6.34 (1H, s),
5 6.82-6.91 (3H, m), 6.99-7.02 (1H, m), 7.10-7.15 (3H, m).
Melting point: 144-146 °C (crystallization solvent: ethyl acetate - n-hexane)

Example 219

10 N-[4-Methyl-3-(4-morpholinylmethyl)-2H-chromen-7-yl][1,1'-biphenyl]-4-carboxamide



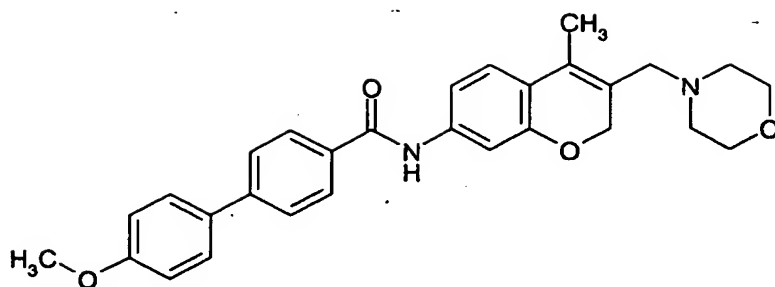
The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using
15 4-methyl-3-(4-morpholinylmethyl)-2H-chromen-7-amine obtained in Reference Example 108.

¹H NMR (DMSO-d₆) δ: 2.01 (3H, s), 2.37 (4H, s), 3.32 (2H, s), 3.57 (4H, s), 4.63 (2H, s), 7.23 (1H, d, J=8.1 Hz),
20 7.38-7.54 (5H, m), 7.76 (2H, d, J=7.5 Hz), 7.84 (2H, d, J=8.1 Hz), 8.04 (2H, d, J=8.1 Hz), 10.27 (1H, s).

Melting point: 162-164 °C (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 220

25 4'-Methoxy-N-[4-methyl-3-(4-morpholinylmethyl)-2H-chromen-7-yl][1,1'-biphenyl]-4-carboxamide



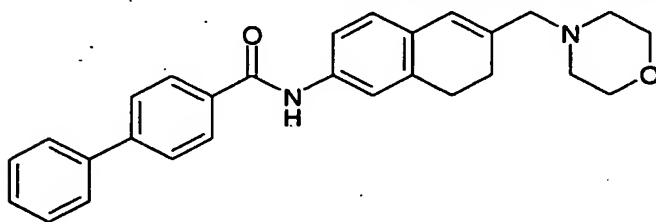
The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using 4-methyl-3-(4-morpholinylmethyl)-2H-chromen-7-amine
 5 obtained in Reference Example 108.

¹H NMR (DMSO-d₆) δ: 2.00 (3H, s), 2.37 (4H, s), 3.11 (2H, s), 3.57 (4H, s), 3.82 (3H, s), 4.63 (2H, s), 7.07 (2H, d, J=8.7 Hz), 7.23 (1H, d, J=8.1 Hz), 7.38-7.40 (2H, m), 7.72 (2H, d, J=8.7 Hz), 7.79 (2H, d, J=8.4 Hz), 8.01 (2H, d, J=8.4
 10 Hz), 10.23 (1H, s).

Melting point: 198-200 °C (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 221

15 N-[6-(4-Morpholinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using 6-(4-morpholinylmethyl)-7,8-dihydro-2-naphthalenamine
 20 obtained in Reference Example 109.

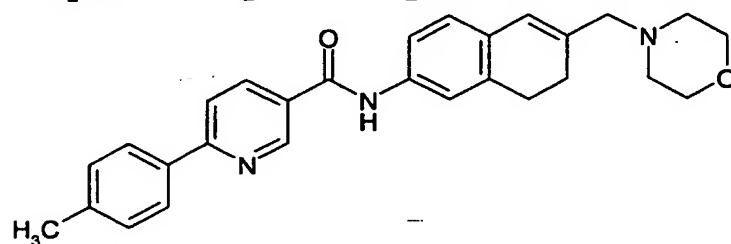
¹H-NMR (CDCl₃) δ: 2.34 (2H, t, J=8.4 Hz), 2.45 (4H, m), 2.85 (2H, t, J=8.4 Hz), 3.06 (2H, s), 3.73 (4H, t, J=4.7 Hz), 6.36 (1H, s), 7.02 (1H, d, J=8.1 Hz), 7.36-7.78 (10H, m),
 25 7.93 (2H, d, J=8.1 Hz).

Melting point: 180-181 °C (crystallization solvent: ethyl acetate - diisopropyl ether)

ethyl acetate - diisopropyl ether)

Example 222

6-(4-Methylphenyl)-N-[6-(4-morpholinylmethyl)-7,8-dihydro-2-naphthalenyl]nicotinamide



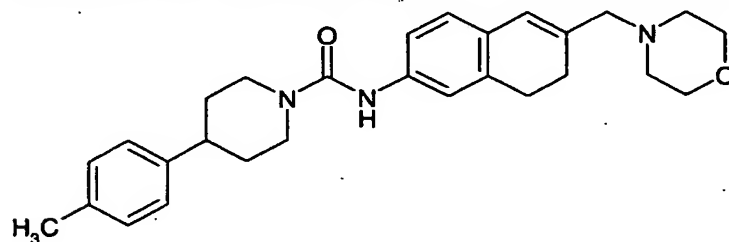
The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using 6-(4-morpholinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 109.

$^1\text{H-NMR}$ (CDCl_3) δ : 2.39 (2H, t, $J=8.4$ Hz), 2.43 (7H, m), 2.85 (2H, t, $J=8.4$ Hz), 3.06 (2H, s), 3.73 (4H, t, $J=4.5$ Hz), 6.36 (1H, s), 7.03 (1H, d, $J=8.1$ Hz), 7.30-7.38 (3H, m), 7.50 (1H, s), 7.76 (1H, s), 7.84 (1H, d, $J=8.1$ Hz), 7.97 (2H, d, $J=8.1$ Hz), 8.24 (1H, dd, $J=8.4$, 2.3 Hz), 9.12 (1H, s).

Melting point: 233-234 °C (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 223

4-(4-Methylphenyl)-N-[6-(4-morpholinylmethyl)-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide



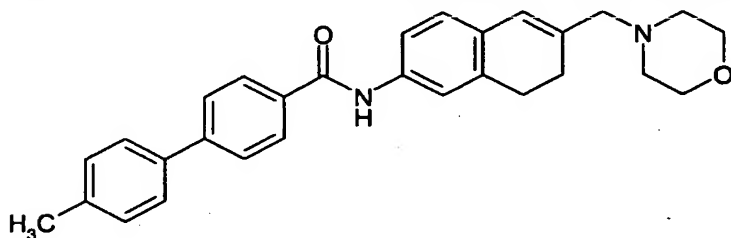
The titled compound was obtained as colorless powders by carrying out the same operation as in Example 99, using 6-(4-morpholinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 109.

¹H-NMR (CDCl₃) δ: 1.65-1.75 (4H, m), 1.90 (2H, m), 2.27-2.43 (7H, m), 2.72 (1H, m), 2.79 (2H, t, J=7.5 Hz), 2.93-3.04 (4H, m), 3.72 (4H, m), 4.20 (2H, d, J=11.7 Hz), 6.31 (1H, s), 6.39 (1H, s), 6.92 (1H, d, J=8.1 Hz), 7.05-7.26 (6H, m).

Melting point: 231-214 °C (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 224

10 4'-Methyl-N-[6-(4-morpholinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using 15 6-(4-morpholinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 109.

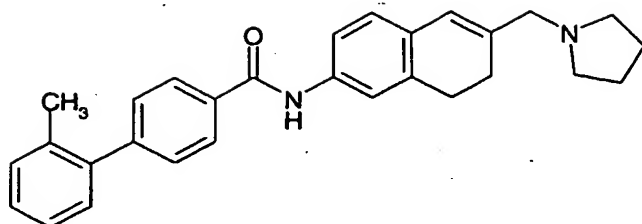
¹H-NMR (CDCl₃) δ: 2.33 (2H, t, J=8.1 Hz), 2.42-2.44 (7H, m), 2.84 (2H, t, J=8.1 Hz), 3.06 (2H, s), 3.72 (4H, t, J=4.2 Hz), 6.36 (1H, s), 7.01 (1H, d, J=8.1 Hz), 7.25-7.29 (2H, m), 7.37 (1H, d, J=8.1 Hz), 7.51-7.54 (3H, m), 7.68 (2H, d, J=8.1 Hz), 7.85 (1H, s), 7.92 (2H, d, J=8.1 Hz).

Melting point: 196-197 °C (crystallization solvent: ethyl acetate - diisopropyl ether)

25 Example 225

2'-Methyl-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide

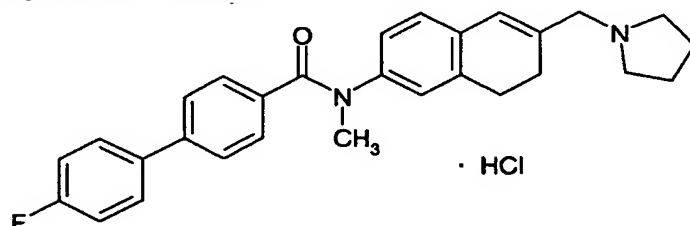
298



The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine
5 obtained in Reference Example 54.
Melting point: 177-178 °C (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 226

10 4'-Fluoro-N-methyl-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide Hydrochloride

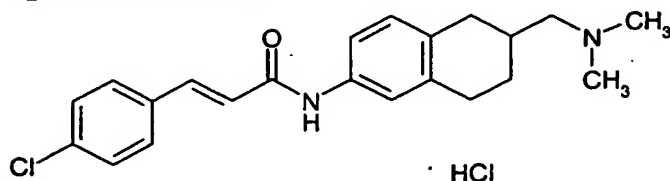


N-Methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine dihydrochloride (315 mg, 1.0 mmol)
15 obtained in Reference Example 113 was dissolved in N,N-dimethylformamide (25 ml). 4-Bromobenzoic acid (402 mg, 2.0 mmol), WSC (383 mg, 2.0 mmol), HOBt (270 mg, 2.0 mmol) and DMAP (244mg, 2.0 mmol) were added to the solution,
20 which was stirred at room temperature for 16 hours. Ethyl acetate and water were added to the reaction mixture, and extraction was conducted. The ethyl acetate layer was concentrated under reduced pressure. The residue was purified by aluminum column chromatography (development
25 solvent; ethyl acetate : n-hexane = 33:67). The eluate was concentrated under reduced pressure, which was dissolved in dimethoxyethane - tetrahydrofuran (10:1, 5.5 ml).

4-Fluorophenylboric acid (73 mg, 0.52 mmol) ,
tetrakis(triphenylphosphine)palladium complex (15 mg,
0.013 mmol) and 2N aqueous sodium carbonate solution (
0.433 ml) were added to the solution, which was refluxed
5 with heating under nitrogen atmosphere at 90°C for 5.5
hours. The reaction mixture was poured into cold water,
and extraction was conducted using ethyl acetate. The
ethyl acetate layer was concentrated, and the residue was
purified by aluminum column chromatography (development
10 solvent; ethyl acetate) . 4N Hydrogen chloride - ethyl
acetate solution was added to the eluate, which was
concentrated under reduced pressure. The resulting
residue was recrystallized from methanol - ethyl acetate,
to give the titled compound (108 mg) .
15 ¹H-NMR (DMSO-d₆) δ : 1.92-1.98 (4H, m), 2.39 (2H, t, J=8.1
Hz), 2.73 (2H, t, J=8.1 Hz), 3.00 (2H, m), 3.35 (3H, m),
3.44 (2H, m), 3.83 (2H, d, J=5.6 Hz), 6.62 (1H, s), 6.92-7.01
(2H, m), 7.11 (1H, s), 7.26 (2H, dd, J=8.9, 5.6 Hz), 7.38
(2H, d, J=8.1 Hz), 7.55 (2H, d, J=8.1 Hz), 7.69 (2H, dd,
20 J=8.9, 5.6 Hz), 10.60 (1H, brs.).
Melting point: 201-203 °C (crystallization solvent :
methanol - diisopropyl ether)
FAB(pos) 441.2 [M+H]⁺

25 Example 227

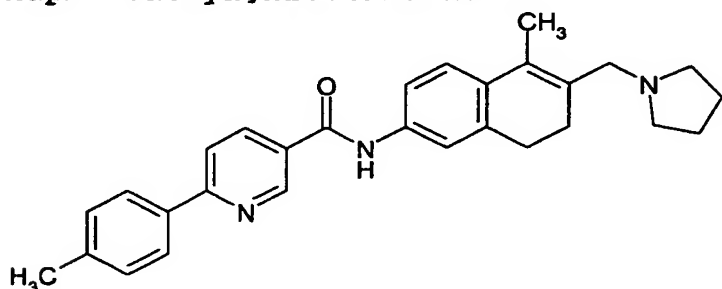
(E)-3-(4-Chlorophenyl)-N-[6-[(dimethylamino)methyl]-
5,6,7,8-tetrahydro-2-naphthalenyl]-2-propenamide
Hydrochloride



30 The titled compound was obtained as colorless powders
by carrying out the same operation as in Example 4.
Melting point: 243-245 °C (crystallization solvent :
methanol - diisopropyl ether)

Example 228

6-(4-Methylphenyl)-N-[5-methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]nicotinamide



The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using 5-methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 69.

Melting point: 175-176 °C (crystallization solvent: ethyl acetate - diisopropyl ether)

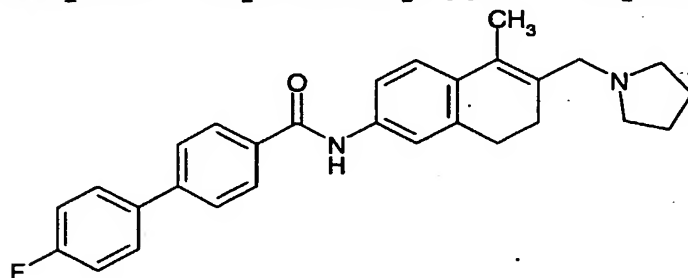
Elemental analysis for C₂₉H₃₀N₃O

Calcd.: C, 79.78; H, 6.93; N, 9.63

Found: C, 79.66; H, 6.97; N, 9.68

Example 229

4'-Fluoro-N-[5-methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using 5-methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 69.

Melting point: 199-201 °C (crystallization solvent: ethyl

acetate - diisopropyl ether)

Elemental analysis for $C_{29}H_{30}FN_2O$

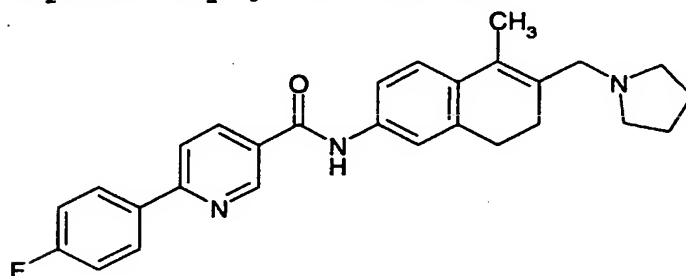
Calcd.: C, 79.06; H, 6.63; N, 6.36

Found: C, 79.01; H, 6.81; N, 6.45

5

Example 230

6-(4-Fluorophenyl)-N-[5-methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]nicotinamide



10

The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using 5-methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 69.

15 Melting point: 204-205 °C (crystallization solvent: ethyl acetate - diisopropyl ether)

Elemental analysis for $C_{28}H_{28}FN_3O$

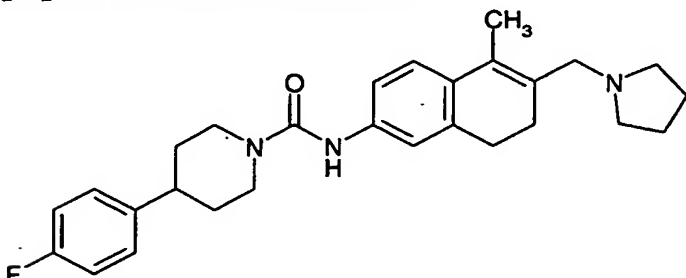
Calcd.: C, 76.17; H, 6.39; N, 9.52

Found: C, 76.03; H, 6.44; N, 9.62

20

Example 231

4-(4-Fluorophenyl)-N-[5-methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide



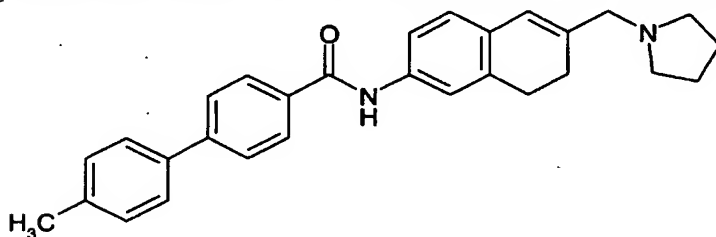
25

The titled compound was obtained as colorless powders by carrying out the same operation as in Example 99, using 5-methyl-6-(1-pyrrolidinymethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 69.

- 5 Melting point: 172-173 °C (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 232

- 10 4'-Methyl-N-[6-(1-pyrrolidinymethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide

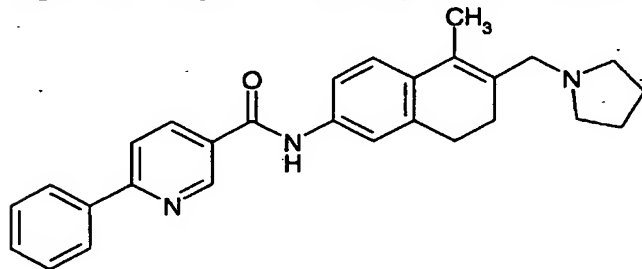


The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using 6-(1-pyrrolidinymethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

15 Melting point: 176-177 °C (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 233

- 20 N-[5-Methyl-6-(1-pyrrolidinymethyl)-7,8-dihydro-2-naphthalenyl]-6-phenylnicotinamide



The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using 5-methyl-6-(1-pyrrolidinymethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 69.

Melting point: 178-179 °C (crystallization solvent: ethyl acetate - diisopropyl ether)

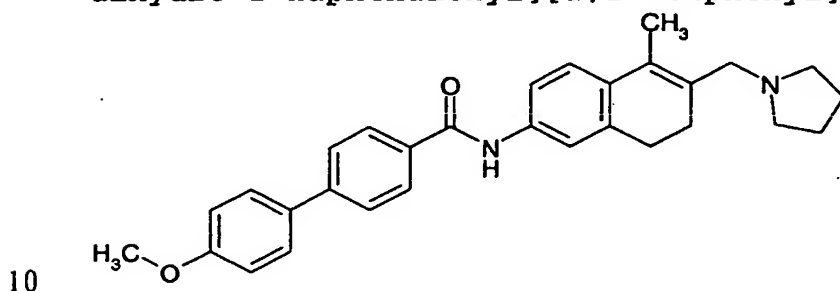
Elemental analysis for $C_{28}H_{29}N_3O$

Calcd.: C, 79.40; H, 6.90; N, 9.92

5 Found: C, 79.13; H, 6.82; N, 10.03

Example 234

4'-Methoxy-N-[5-methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using 5-methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 69.

15 $^1\text{H-NMR}$ (CDCl_3) δ : 1.78 (4H, m), 2.10 (3H, s), 2.37 (2H, t, $J=8.1$ Hz), 2.53 (4H, m), 2.76 (2H, t, $J=8.1$ Hz), 3.28 (2H, s), 3.87 (3H, s), 7.01 (1H, d, $J=8.6$ Hz), 7.27 (2H, d, $J=7.8$ Hz), 7.46 (1H, d, $J=7.8$ Hz), 7.48 (1H, s), 7.57 (2H, d, $J=8.6$ Hz), 7.66 (2H, d, $J=8.6$ Hz), 7.81 (1H, s), 7.92 (2H, d, $J=7.8$ Hz).

Melting point: 179-180 °C (crystallization solvent: ethyl acetate - diisopropyl ether)

Elemental analysis for $C_{30}H_{32}N_2O_2$

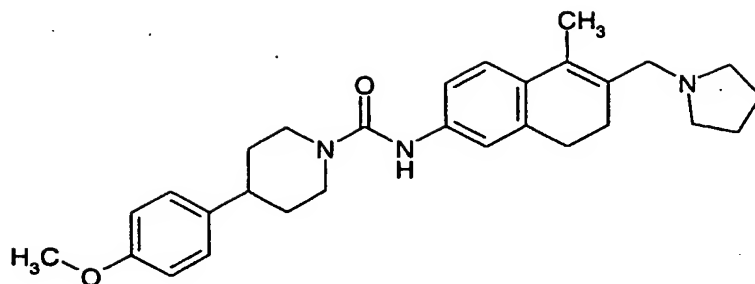
Calcd.: C, 79.61; H, 7.13; N, 6.19

25 Found: C, 79.35; H, 7.28; N, 6.24

Example 235

4-(4-Methoxyphenyl)-N-[5-methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide

30



The titled compound was obtained as colorless powders by carrying out the same operation as in Example 99, using 5-methyl-6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 69.

¹H-NMR (CDCl₃) δ: 1.67 (2H, dd, J=13.4, 4.0 Hz), 1.78 (4H, m), 1.89 (2H, d, J=11.4 Hz), 2.07 (3H, s), 2.34 (2H, t, J=7.5 Hz), 2.52 (4H, m), 2.68-2.73 (3H, m), 2.98 (2H, t, J=7.5 Hz), 3.26 (2H, s), 3.80 (3H, s), 4.20 (2H, d, J=13.4 Hz), 6.36 (1H, s), 6.86 (2H, d, J=8.4 Hz), 7.12-7.20 (5H, m).
Melting point: 163-164 °C (crystallization solvent: ethyl acetate - diisopropyl ether)

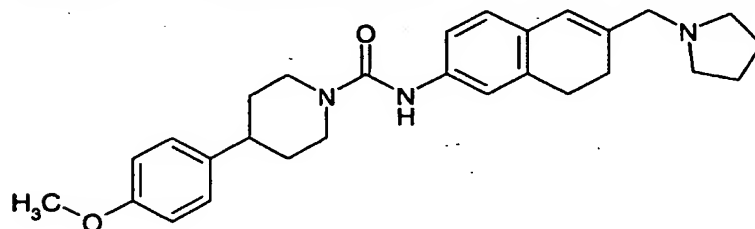
Elemental analysis for C₂₈H₃₇N₃O₂

Calcd.: C, 75.13; H, 8.33; N, 9.39

Found: C, 74.96; H, 8.14; N, 9.10

Example 236

4-(4-Methoxyphenyl)-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide



The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using 6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

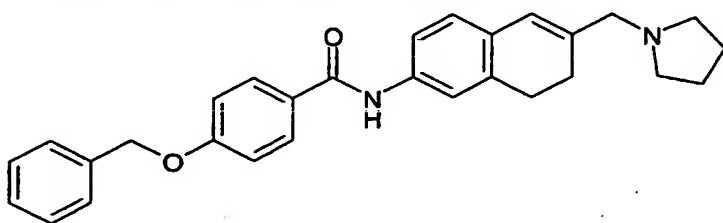
¹H-NMR (CDCl₃) δ: 1.61-1.91 (8H, m), 2.31 (2H, t, J=8.1 Hz), 2.54 (4H, m), 2.73-2.81 (3H, m), 2.98 (2H, t, J=7.8 Hz),

3.16 (2H, s), 3.79 (3H, s), 4.20 (2H, d, J=13.1 Hz), 6.31 (1H, s), 6.36 (1H, s), 6.86 (2H, d, J=8.6 Hz), 7.06-7.20 (5H, m).

Melting point: 175-176 °C (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 237

4-(Benzyloxy)-N-[6-(1-pyrrolidinymethyl)-7,8-dihydro-2-naphthalenyl]benzamide



The titled compound was obtained as colorless powders by carrying out the same operation as in Example 1, using 6-(1-pyrrolidinymethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54.

Melting point: 174-175 °C (crystallization solvent: ethyl acetate - diisopropyl ether)

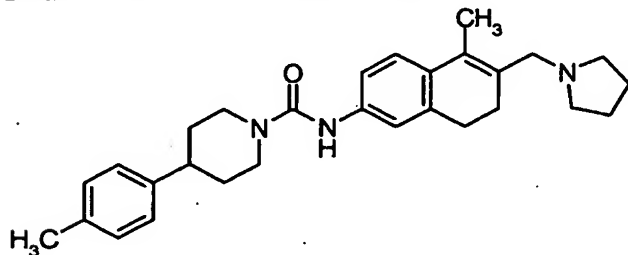
Elemental analysis for $C_{28}H_{30}N_2O_2$

Calcd.: C, 78.84; H, 7.09; N, 6.87

Found: C, 79.06; H, 6.99; N, 6.41

Example 238

4-(4-Methylphenyl)-N-[5-methyl-6-(1-pyrrolidinymethyl)-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide



The titled compound was obtained by carrying out the same operation as in Example 99, using 5-methyl-6-(1-

pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine
obtained in Reference Example 69.

¹H-NMR (CDCl₃) δ: 1.65-1.78 (6H, m), 1.90 (2H, d, J=12.9 Hz), 2.07 (3H, s), 2.33-2.37 (5H, m), 2.53 (4H, m),
5 2.68-2.74 (3H, m), 2.99 (2H, m), 3.27 (2H, s), 4.21 (2H, d, J=13.2 Hz), 6.37 (1H, s), 7.09-7.21 (7H, m).

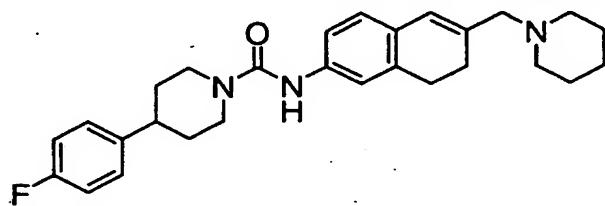
Melting point: 159-160 °C (crystallization solvent:
ethyl acetate - diisopropyl ether)

FAB(pos) 444.3 [M+H]⁺

10

Example 239

4-(4-Fluorophenyl)-N-[6-(1-piperidinylmethyl)-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide



15

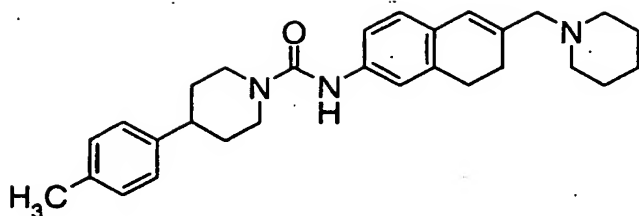
The titled compound was obtained by carrying out the same operation as in Example 99, using 6-(1-piperidinylmethyl)-7,8-dihydro-2-naphthalenamine dihydrochloride obtained in Reference Example 114.

¹H-NMR (CDCl₃) δ: 1.43 (2H, m), 1.56-1.75 (6H, m), 1.89 (2H, d, J=12.3 Hz), 2.27-2.36 (6H, m), 2.70 (1H, m), 2.78 (2H, t, J=7.5 Hz), 2.88-3.00 (4H, m), 4.20 (2H, d, J=13.2 Hz),
20 6.29 (1H, s), 6.38 (1H, s), 6.91-7.08 (4H, m), 7.14-7.20 (3H, m).

Melting point: 194 -195 °C (crystallization solvent:
25 ethyl acetate - diisopropyl ether)

Example 240

4-(4-Methylphenyl)-N-[6-(1-piperidinylmethyl)-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide



The titled compound was obtained by carrying out the same operation as in Example 99, using 6-(1-piperidinylmethyl)-7,8-dihydro-2-naphthalenamine

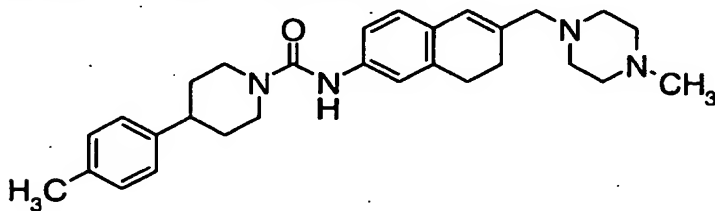
5 dihydrochloride obtained in Reference Example 114.

¹H-NMR (CDCl₃) δ: 1.43 (2H, m), 1.56-1.74 (6H, m), 1.90 (2H, d, J=12.0 Hz), 2.27-2.36 (9H, m), 2.69 (1H, m), 2.79 (2H, t, J=8.1 Hz), 2.94-3.01 (4H, m), 4.19 (2H, d, J=13.2 Hz), 6.29 (1H, s), 6.35 (1H, s), 6.93 (2H, d, J=8.1 Hz), 7.05-7.26
10 (5H, m).

Melting point: 209 -210 °C (crystallization solvent: ethyl acetate - diisopropyl ether)

Example 241

15 4-(4-Methylphenyl)-N-[6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide



The titled compound was obtained by carrying out the same operation as in Example 99, using 6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenamine
20 obtained in Reference Example 106.

¹H NMR (CDCl₃) δ: 1.62-1.77 (2H, m), 1.90 (2H, d, J=12.0 Hz), 2.28 (2H, t, J=8.1 Hz), 2.29 (3H, s), 2.33 (3H, s),
25 2.46 (8H, bs), 2.64-2.73 (1H, m), 2.79 (2H, t, J=8.1 Hz), 2.96 (2H, d, J=10.5 Hz), 3.05 (2H, s), 4.19 (2H, d, J=13.5 Hz), 6.31 (1H, s), 6.34 (1H, s), 6.93 (1H, d, J=8.4 Hz), 7.04-7.16 (5H, m), 7.23 (1H, s).

Melting point: 214-216 °C (crystallization solvent:
tetrahydrofuran - n-hexane)

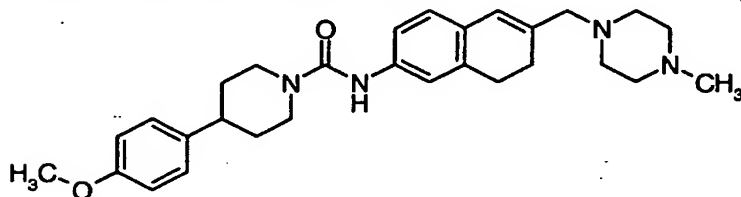
Elemental analysis for $C_{29}H_{38}N_4O$

Calcd.: C, 75.94; H, 8.35; N, 12.22.

5 Found: C, 75.67; H, 8.47; N, 12.27.

Example 242

4-(4-Methoxyphenyl)-N-[6-[(4-methyl-1-
piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl]-1-
10 piperidinecarboxamide



The titled compound was obtained by carrying out the
same operation as in Example 99, using 6-[(4-methyl-1-
piperazinyl)methyl]-7,8-dihydro-2-naphthalenamine
15 obtained in Reference Example 106.

¹H NMR (CDCl₃) δ: 1.68-1.76 (2H, m), 1.89 (2H, d, J=1.1
Hz), 2.29 (2H, t, J=8.1 Hz), 2.29 (3H, s), 2.46 (8H, bs),
2.64-2.71 (1H, m), 2.79 (2H, t, J=8.1 Hz), 2.82-3.03 (2H,
m), 3.05 (2H, s), 3.80 (3H, s), 4.19 (2H, d, J=12.6 Hz),
20 6.31 (1H, s), 6.34 (1H, s), 6.87 (2H, d, J=8.7 Hz), 6.93
(1H, d, J=8.4 Hz), 7.06 (1H, dd, J=8.1, 2.1 Hz), 7.14 (2H,
d, J=8.7 Hz), 7.23 (1H, s).

Melting point: 198-200 °C (crystallization solvent:
tetrahydrofuran - n-hexane)

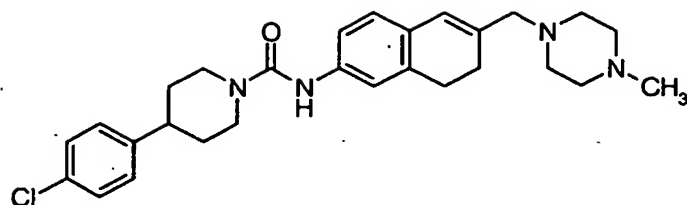
25 Elemental analysis for $C_{29}H_{38}N_4O_2$

Calcd.: C, 73.38; H, 8.07; N, 11.80.

Found: C, 73.04; H, 7.95; N, 11.67.

Example 243

30 4-(4-Chlorophenyl)-N-[6-[(4-methyl-1-
piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl]-1-
piperidinecarboxamide



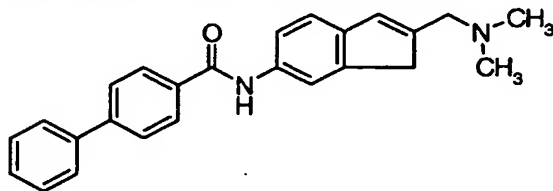
The titled compound was obtained by carrying out the same operation as in Example 99, using 6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenamine

obtained in Reference Example 106.
¹H NMR (CDCl₃) δ: 1.64-1.76 (2H, m), 1.90 (2H, d, J=11.1 Hz), 2.29 (2H, t, J=8.1 Hz), 2.29 (3H, s), 2.46 (8H, bs), 2.66-2.72 (1H, m), 2.79 (2H, t, J=8.1 Hz), 2.81-3.03 (2H, m), 3.05 (2H, s), 4.20 (2H, d, J=12.6 Hz), 6.31 (1H, s), 6.34 (1H, s), 6.93 (1H, d, J=7.8 Hz), 7.04-7.07 (1H, m), 7.14 (2H, d, J=8.4 Hz), 7.22 (1H, s), 7.28 (2H, d, J=8.4 Hz).

Melting point: 201-203 °C (crystallization solvent: tetrahydrofuran - n-hexane)

Example 244

N-[2-[(Dimethylamino)methyl]-1H-inden-6-yl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Example 1, using 2-[(dimethylamino)methyl]-1H-inden-6-amine obtained in Reference Example 116.

Elemental analysis for C₂₅H₂₄N₂O · 0.5H₂O

Calcd.: C, 79.55; H, 6.68; N, 7.42.

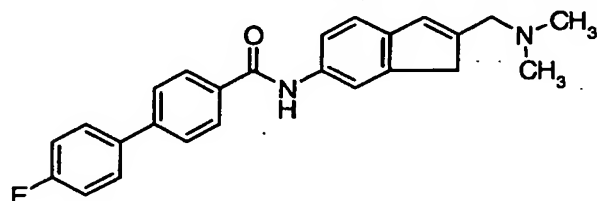
Found: C, 79.38; H, 6.76; N, 7.34.

Melting point: 187-189 °C (crystallization solvent: ethyl acetate - diisopropyl ether)

FAB(pos) 369.2 [M+H]⁺

Example 245

N-[2-[(Dimethylamino)methyl]-1H-inden-6-yl]-4'-
5 fluoro[1,1'-biphenyl]-4-carboxamide



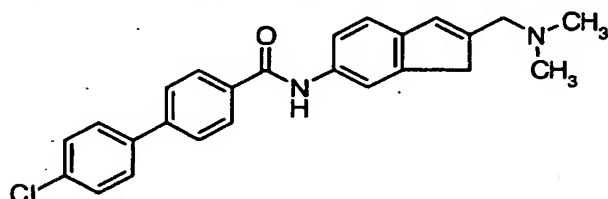
The titled compound was obtained by carrying out the
same operation as in Example 1, using 2-
[(dimethylamino)methyl]-1H-inden-6-amine obtained in
10 Reference Example 116.

Melting point: 209-211 °C (crystallization solvent: ethyl
acetate - diisopropyl ether)

FAB(pos) 387.2 [M+H]⁺

15 Example 246

4'-Chloro-N-[2-[(dimethylamino)methyl]-1H-inden-6-
yl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the
20 same operation as in Example 1, using 2-
[(dimethylamino)methyl]-1H-inden-6-amine obtained in
Reference Example 116.

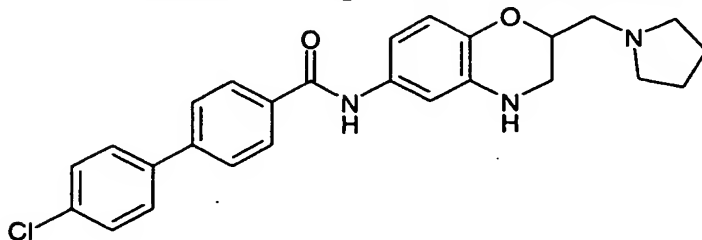
Melting point: 218-220 °C (crystallization solvent: ethyl
acetate - diisopropyl ether)

25 FAB(pos) 403.2 [M+H]⁺

Example 247

4'-Chloro-N-[2-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-

1,4-benzoxazin-6-yl][1,1'-biphenyl]-4-carboxamide



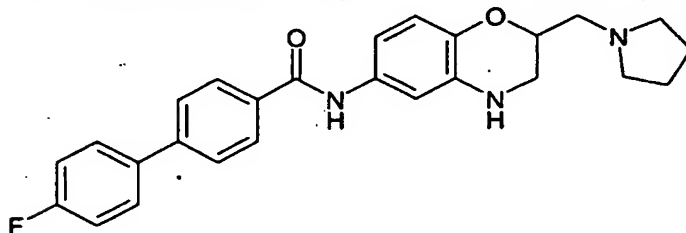
The titled compound was obtained by carrying out the same operation as in Example 1, using 6-amino-2-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-1,4-benzoxazine obtained in Reference Example 117.

¹H-NMR (CDCl₃) δ: 1.70-1.90 (4H, m), 2.50-2.70 (4H, m), 2.73 (2H, d, J=6.0Hz), 3.18-3.24 (1H, m), 3.45-3.49 (1H, m), 3.87 (1H, brs), 4.26-4.28 (1H, m), 6.61 (1H, dd, J=2.7, 8.4 Hz), 6.80 (1H, d, J=8.4 Hz), 7.26 (1H, d, J=2.7 Hz), 7.44 (2H, d, J=8.4 Hz), 7.55 (2H, d, J=8.4 Hz), 7.64 (2H, d, J=8.1 Hz), 7.71 (1H, s), 7.91 (2H, d, J=8.1 Hz).

Melting point: 221-222 °C (crystallization solvent: diisopropyl ether)

Example 248

4'-Fluoro-N-[2-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-1,4-benzoxazin-6-yl][1,1'-biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Reference Example 1, using 6-amino-2-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-1,4-benzoxazine obtained in Reference Example 117.

¹H-NMR (CDCl₃) δ: 1.70-1.90 (4H, m), 2.50-2.70 (4H, m), 2.73 (2H, d, J = 6.3Hz), 3.18-3.24 (1H, m), 3.45-3.49 (1H, m), 3.88 (1H, brs), 4.24-4.30 (1H, m), 6.62 (1H, dd, J=2.7, 8.4 Hz), 6.80 (1H, d, J=8.4 Hz), 7.13-7.19 (2H, m), 7.26 (1H,

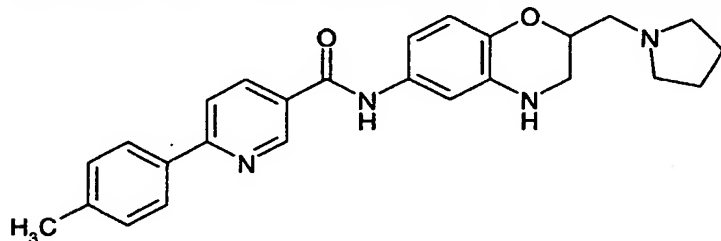
d, J=2.7 Hz), 7.56-7.60 (2H, m), 7.63 (2H, d, J=8.4 Hz), 7.71 (1H, s), 7.90 (2H, d, J=8.4 Hz).

Melting point: 204-206 °C (crystallization solvent: diisopropyl ether)

5

Example 249

6-(4-Methylphenyl)-N-[2-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-1,4-benzoxazin-6-yl]nicotinamide



10

The titled compound was obtained by carrying out the same operation as in Reference Example 1, using 6-amino-2-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-1,4-benzoxazine obtained in Reference Example 117.

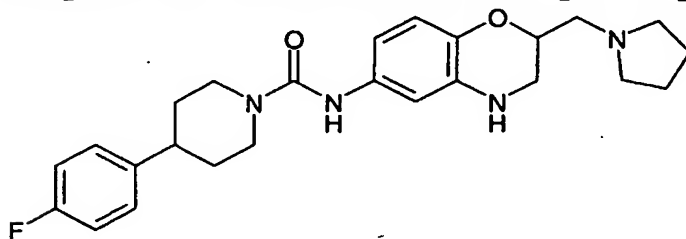
¹H-NMR (CDCl₃) δ: 1.70-1.85 (4H, m), 2.43 (3H, s), 2.50-2.70 (4H, m), 2.74 (2H, d, J=6.3Hz), 3.19-3.25 (1H, m), 3.45-3.49 (1H, m), 3.90 (1H, brs), 4.27-4.29 (1H, m), 6.63 (1H, dd, J=2.4, 8.7 Hz), 6.81 (1H, d, J=8.7 Hz), 7.26 (1H, d, J=2.7 Hz), 7.31 (2H, d, J=8.1 Hz), 7.67 (1H, s), 7.81 (1H, d, J=8.1 Hz), 7.93 (2H, d, J=7.8Hz), 8.21 (1H, dd, J=2.4, 8.4 Hz), 9.09 (1H, d, J=2.4 Hz).

20

Melting point: 207-208 °C (crystallization solvent: diisopropyl ether)

Example 250

4-(4-Fluorophenyl)-N-[2-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-1,4-benzoxazin-6-yl]-1-piperidinecarboxamide



25

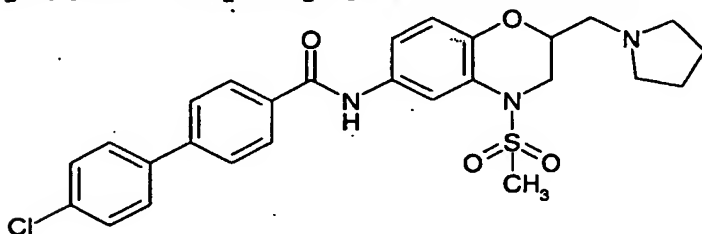
The titled compound was obtained by carrying out the same operation as in Reference Example 1, using 6-amino-2-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-1,4-benzoxazine obtained in Reference Example 117.

5 ¹H-NMR (CDCl₃) δ: 1.60-1.90 (8H, m), 2.50-2.70 (5H, m), 2.71 (2H, d, J=6.3Hz), 2.91-3.00 (2H, m), 3.15-3.21 (1H, brs), 3.42-3.45 (1H, m), 3.77 (1H, brs), 4.15-4.25 (3H, m), 6.20 (1H, s), 6.38 (1H, dd, J=2.1, 8.4 Hz), 6.73 (1H, d, J=8.4 Hz), 6.91 (1H, d, J=2.1 Hz), 6.97-7.03 (2H, m), 7.14-7.19 (2H, m).

Melting point: 192-195 °C (crystallization solvent: diisopropyl ether)

Example 251

15 4'-Chloro-N-[4-(methylsulfonyl)-2-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-1,4-benzoxazin-6-yl][1,1'-biphenyl]-4-carboxamide



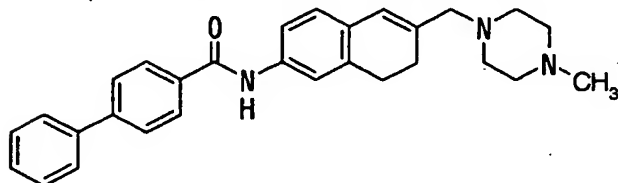
20 The titled compound was obtained by carrying out the same operation as in Reference Example 1, using 6-amino-4-(methylsulfonyl)-2-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-1,4-benzoxazine obtained in Reference Example 118.

25 ¹H-NMR (CDCl₃) δ: 1.75-1.85 (4H, m), 2.55-2.70 (4H, m), 2.78 (2H, d, J=6.0Hz), 3.04 (3H, s), 3.27-3.34 (1H, m), 4.24-4.31 (1H, m), 4.31-4.35 (1H, m), 6.98 (1H, d, J=8.7 Hz), 7.45 (2H, d, J=9.0 Hz), 7.50-7.60 (1H, m), 7.53 (2H, d, J=9.0 Hz), 7.67 (2H, d, J=8.4 Hz), 7.84 (1H, s), 7.84 (1H, brs), 7.94 (2H, d, J=8.4 Hz).

30 Melting point: 203-204 °C (crystallization solvent: diisopropyl ether)

Example 252

N-[6-[(4-Methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



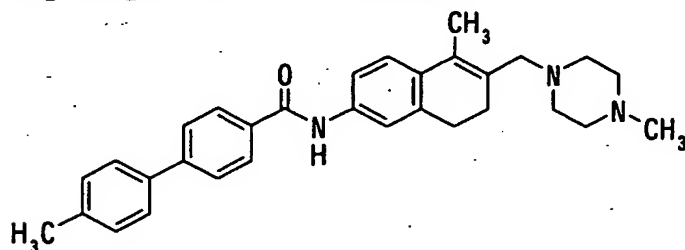
5 The titled compound was obtained by carrying out the same operation as in Reference Example 1, using 6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 106.

¹H NMR (CDCl₃) δ: 2.31 (3H, s), 2.33 (2H, t, J=8.1 Hz), 2.49
10 (8H, bs), 2.84 (2H, t, J=8.1 Hz), 3.07 (2H, s), 6.36 (1H, s), 7.02 (1H, d, J=8.1 Hz), 7.35-7.52 (5H, m), 7.63 (2H, d, J=8.1 Hz), 7.71 (2H, d, J=8.1 Hz), 7.80 (1H, s), 7.94 (2H, d, J=8.1 Hz).

Melting point: 196-198 °C (crystallization solvent:
15 ethyl acetate)

Example 253

4'-Methyl-N-[5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-
20 biphenyl]-4-carboxamide



The titled compound was obtained by carrying out the same operation as in Reference Example 1, using 5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-
25 2-naphthalenamine obtained in Reference Example 115.

¹H NMR (CDCl₃) δ: 2.08 (3H, s), 2.29 (3H, s), 2.34 (2H, t, J=7.8 Hz), 2.42 (3H, s), 2.45 (8H, bs), 2.75 (2H, t, J=7.8 Hz), 3.16 (2H, s), 7.26-7.30 (3H, m), 7.44 (1H, d, J=8.4

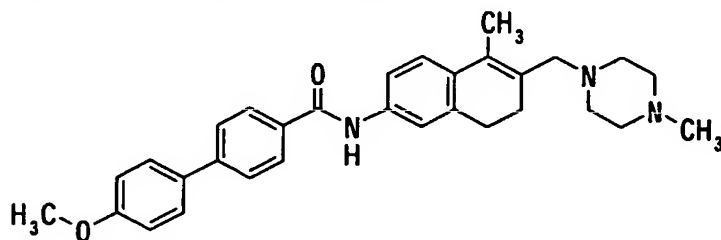
Hz), 7.53-7.55 (3H, m), 7.70 (2H, d, J=8.4 Hz), 8.00 (1H, s), 7.93 (2H, d, J=8.4 Hz).

Melting point: 212-214 °C (crystallization solvent: ethyl acetate)

5

Example 254

4'-Methoxy-N-[5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



10

The titled compound was obtained by carrying out the same operation as in Reference Example 1, using 5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 115.

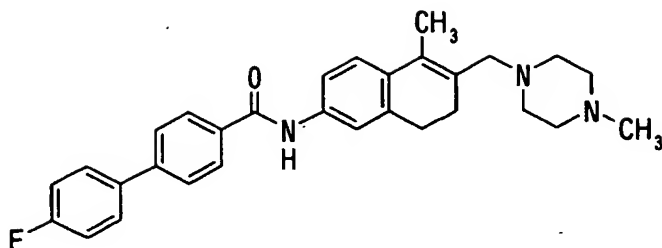
15 ¹H NMR (CDCl₃) δ: 2.08 (3H, s), 2.29 (3H, s), 2.34 (2H, t, J=7.8 Hz), 2.45 (8H, bs), 2.75 (2H, t, J=7.8 Hz), 3.16 (2H, s), 3.87 (3H, s), 7.01 (2H, d, J=8.1 Hz), 7.27 (1H, d, J=8.4 Hz), 7.44 (1H, d, J=8.4 Hz), 7.51 (1H, s), 7.58 (2H, d, J=8.4 Hz), 7.67 (2H, d, J=8.4 Hz), 7.81 (1H, s), 7.92 (2H, d, J=8.4 Hz).

20

Melting point: 215-217 °C (crystallization solvent: ethyl acetate)

Example 255

25 4'-Fluoro-N-[5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



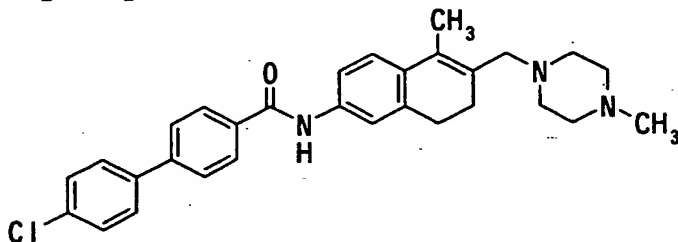
The titled compound was obtained by carrying out the same operation as in Reference Example 1, using 5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 115.

¹H NMR (CDCl₃) δ: 2.08 (3H, s), 2.29 (3H, s), 2.34 (2H, t, J=7.8 Hz), 2.46 (8H, bs), 2.75 (2H, t, J=7.8 Hz), 3.16 (2H, s), 7.17 (2H, d, J=8.4 Hz), 7.28 (1H, d, J=8.4 Hz), 7.44 (1H, d, J=8.4 Hz), 7.51 (1H, s), 7.57-7.62 (2H, m), 7.66 (2H, d, J=8.4 Hz), 7.82 (1H, s), 7.94 (2H, d, J=8.4 Hz).

Melting point: 233-235 °C (crystallization solvent: ethyl acetate)

Example 256

4'-Chloro-N-[5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



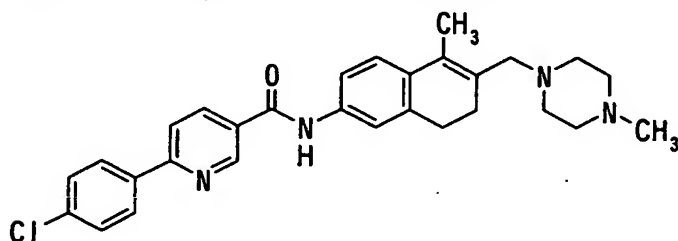
The titled compound was obtained by carrying out the same operation as in Reference Example 1, using 5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 115.

¹H NMR (CDCl₃) δ: 2.08 (3H, s), 2.29 (3H, s), 2.34 (2H, t, J=7.8 Hz), 2.46 (8H, bs), 2.75 (2H, t, J=7.8 Hz), 3.16 (2H, s), 7.28 (1H, d, J=8.4 Hz), 7.43-7.47 (3H, m), 7.51 (1H, s), 7.56 (2H, d, J=8.4 Hz), 7.67 (2H, d, J=8.4 Hz), 7.80 (1H, s), 7.94 (2H, d, J=8.4 Hz).

Melting point: 216-218 °C (crystallization solvent: ethyl acetate)

Example 257

- 5 6-(4-Chlorophenyl)-N-[5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl]nicotinamide



- 10 The titled compound was obtained by carrying out the same operation as in Reference Example 1, using 5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 115.

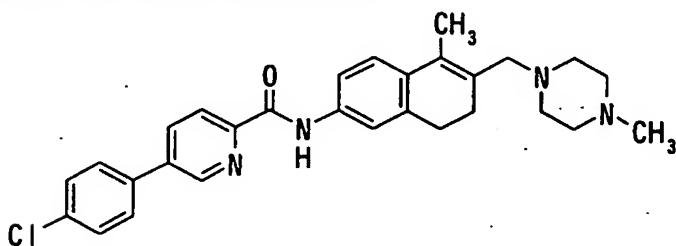
- 15 ¹H NMR (CDCl₃) δ: 2.09 (3H, s), 2.29 (3H, s), 2.35 (2H, t, J=8.1 Hz), 2.46 (8H, bs), 2.75 (2H, t, J=8.1 Hz), 3.16 (2H, s), 7.28 (1H, d, J=8.4 Hz), 7.43-7.50 (4H, m), 7.83 (2H, d, J=8.4 Hz), 8.01 (2H, d, J=8.4 Hz), 8.27 (1H, d, J=8.4 Hz), 9.13 (1H, s).

Melting point: 219-221 °C (crystallization solvent: ethyl acetate)

20

Example 258

- 5-(4-Chlorophenyl)-N-[5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl]-2-pyridinecarboxamide



25

The titled compound was obtained by carrying out the same operation as in Reference Example 1, using 5-

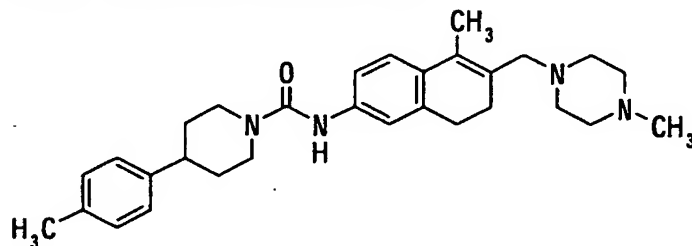
methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 115.

¹H NMR (CDCl₃) δ: 2.09 (3H, s), 2.29 (3H, s), 2.35 (2H, t, J=8.1 Hz), 2.45 (8H, bs), 2.77 (2H, t, J=8.1 Hz), 3.16 (2H, s), 7.30 (1H, d; J=8.1 Hz), 7.49-7.63 (6H, m), 8.05 (1H, dd, J=2.4 Hz, 8.4 Hz), 8.36 (1H, d, J=8.1 Hz), 8.79 (1H, d, J=1.2 Hz), 9.97 (1H, s).

Melting point: 177-179 °C (crystallization solvent: ethyl acetate)

Example 259

N-[5-Methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl]-4-(4-methylphenyl)-1-piperidinecarboxamide



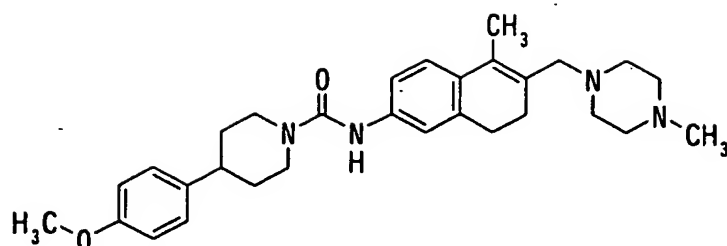
The titled compound was obtained by carrying out the same operation as in Reference Example 99, using 5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 115.

¹H NMR (CDCl₃) δ: 1.60-1.78 (4H, m), 2.05 (3H, s), 2.28 (3H, s), 2.29 (2H, t, J=8.1 Hz), 2.33 (3H, s), 2.46 (8H, bs), 2.65-2.72 (3H, m), 2.93-3.03 (2H, m), 3.13 (2H, s), 4.18-4.23 (2H, m), 6.40 (1H, s), 7.09-7.24 (7H, m).

Melting point: 176-178 °C (crystallization solvent: ethyl acetate-hexane)

Example 260

4-(4-Methoxyphenyl)-N-[5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide



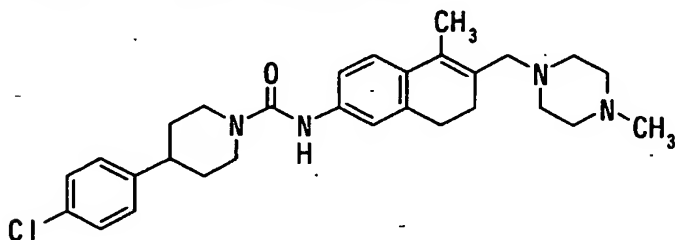
The titled compound was obtained by carrying out the same operation as in Reference Example 99, using 5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 115.

¹H NMR (CDCl₃) δ: 1.68-1.92 (4H, m), 2.05 (3H, s), 2.28 (3H, s), 2.29 (2H, t, J=8.1 Hz), 2.45 (8H, bs), 2.67-2.72 (3H, m), 2.95-3.02 (2H, m), 3.14 (2H, s), 3.80 (3H, s), 4.18-4.22 (2H, m), 6.36 (1H, s), 6.87 (2H, d, J=8.4 Hz), 7.12-7.21 (5H, m).

Melting point: 175-177 °C (crystallization solvent: ethyl acetate)

Example 261

4-(4-Chlorophenyl)-N-[5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide



The titled compound was obtained by carrying out the same operation as in Reference Example 99, using 5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 115.

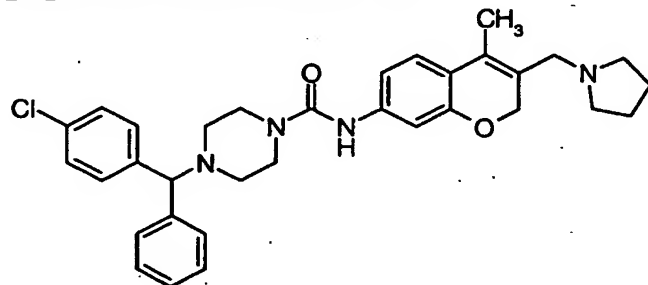
¹H NMR (CDCl₃) δ: 1.67-1.92 (4H, m), 2.05 (3H, s), 2.28 (3H, s), 2.29 (2H, t, J=8.1 Hz), 2.45 (8H, bs), 2.67-2.72 (3H, m), 2.95-3.02 (2H, m), 3.14 (2H, s), 4.18-4.23 (2H, m), 6.36 (1H, s), 7.13-7.30 (7H, m).

Melting point: 141-143 °C (crystallization solvent: ethyl acetate)

ethyl acetate)

Example 262

4-[(4-Chlorophenyl)(phenyl)methyl]-N-[4-methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-yl]-1-piperazinecarboxamide



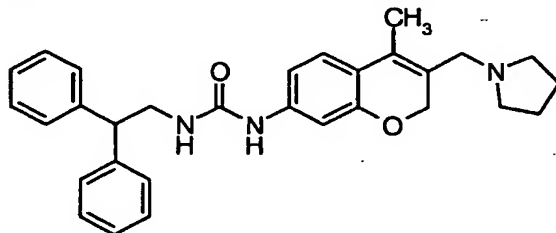
The titled compound was obtained by carrying out the same operation as in Reference Example 99, using 4-methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-amine obtained in Reference Example 107.

^1H NMR (CDCl_3) δ : 1.76 (4H, s), 2.01 (3H, s), 2.42 (4H, t, $J=5.1$ Hz), 2.49 (4H, s), 3.22 (2H, s), 3.48 (4H, t, $J=5.1$ Hz), 4.24 (1H, s), 4.68 (2H, s), 6.23 (1H, s), 6.77 (1H, s), 6.96 (1H, d, $J=8.7$ Hz), 7.09 (1H, d, $J=8.7$ Hz), 7.19-7.61 (9H, m).

Melting point: 104-106 °C (crystallization solvent: ethyl acetate - n-hexane)

Example 263

N-(2,2-Diphenylethyl)-N'-[4-methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-yl]urea



The titled compound was obtained by carrying out the same operation as in Reference Example 99, using 4-methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-amine

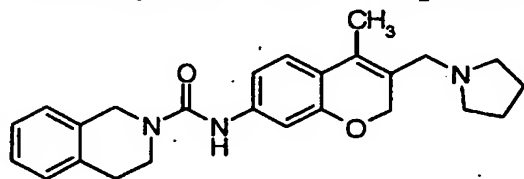
obtained in Reference Example 107.

¹H NMR (CDCl₃) δ: 1.76 (4H, s), 1.99 (3H, s), 2.49 (4H, s),
3.22 (2H, s), 3.83 (2H, t, J=7.8 Hz), 4.18 (1H, t, J=7.8
Hz), 4.66 (2H, s), 4.96 (1H, s), 6.48 (1H, s), 6.57 (1H,
5 s), 6.69 (1H, d, J=8.1 Hz), 6.98 (1H, d, J=8.1 Hz), 7.20-7.30
(10H, m).

Melting point: 166-168 °C (crystallization solvent:
ethyl acetate - n-hexane)

10 Example 264

N-[4-Methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-yl]-
3,4-dihydro-2(1H)-isoquinolinecarboxamide



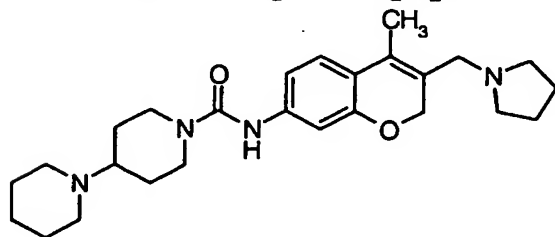
The titled compound was obtained by carrying out the
15 same operation as in Reference Example 99, using 4-
methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-amine
obtained in Reference Example 107.

¹H NMR (CDCl₃) δ: 1.76 (4H, s), 2.02 (3H, s), 2.49 (4H, s),
2.92 (2H, t, J=6.0 Hz), 3.23 (2H, s), 3.71 (2H, t, J=6.0 Hz),
20 4.65 (2H, s), 4.68 (2H, s), 6.43 (1H, s), 6.86 (1H, d, J=1.8
Hz), 7.02-7.22 (6H, m).

Melting point: 135-137 °C (crystallization solvent:
ethyl acetate - n-hexane)

25 Example 265

N-[4-Methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-yl]-
4-(1-piperidiny)-1-piperidinecarboxamide

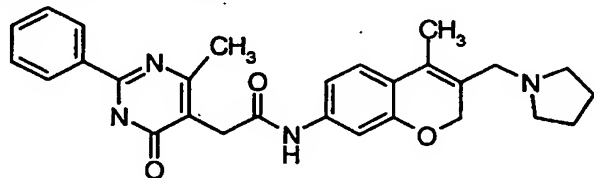


The titled compound was obtained by carrying out the same operation as in Reference Example 99, using 4-methyl-3-(1-pyrrolidinymethyl)-2H-chromen-7-amine obtained in Reference Example 107.

- 5 ¹H NMR (CDCl₃) δ: 1.27-1.89 (14H, m), 2.02 (3H, s), 2.49-2.51 (9H, m), 2.83-2.90 (2H, m), 3.23 (2H, s), 4.08-4.12 (2H, m), 4.68 (2H, s), 6.31 (1H, s), 6.80 (1H, d, J=2.4 Hz), 6.98 (1H, dd, J=2.4 Hz, 8.4 Hz), 7.09 (1H, d, J=8.4 Hz).
- 10 Melting point: 98-100 °C (crystallization solvent: ethyl acetate - n-hexane)

Example 266

- 2-(4-Methyl-6-oxo-2-phenyl-1,6-dihydro-5-pyrimidinyl)-
15 N-[4-methyl-3-(1-pyrrolidinymethyl)-2H-chromen-7-yl]acetamide

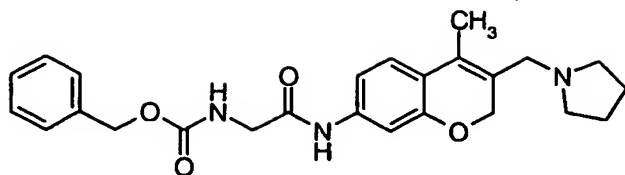


The titled compound was obtained by carrying out the same operation as in Reference Example 1, using 4-methyl-3-(1-pyrrolidinymethyl)-2H-chromen-7-amine obtained in Reference Example 107.

- 20 ¹H NMR (CDCl₃) δ: 1.76 (4H, s), 1.98 (3H, s), 2.49 (4H, s), 2.61 (3H, s), 3.22 (2H, s), 3.65 (2H, s), 4.65 (2H, s), 6.86-7.00 (4H, m), 7.54 (3H, s), 8.01 (2H, s), 8.87 (1H, s).
- 25 Melting point: 255-257 °C (crystallization solvent: ethyl acetate - n-hexane)

Example 267

- Benzyl 2-[[4-methyl-3-(1-pyrrolidinymethyl)-2H-chromen-7-yl]amino]-2-oxoethylcarbamate
30



The titled compound was obtained by carrying out the same operation as in Reference Example 1, using 4-methyl-3-(1-pyrrolidinylmethyl)-2H-chromen-7-amine obtained in Reference Example 107.

^1H NMR (CDCl_3) δ : 1.78 (4H, s), 2.03 (3H, s), 2.53 (4H, s), 3.26 (2H, s), 3.99 (2H, d, $J=4.8$ Hz), 4.71 (2H, s), 5.17 (2H, s), 5.50 (1H, bs), 7.00-7.14 (4H, m), 7.36 (5H, s), 7.80 (1H, bs).

Melting point: 143-145 $^{\circ}\text{C}$ (crystallization solvent: ethyl acetate - n-hexane)

Preparation Example 1

	(1) Compound obtained in	
15	Reference Example 25	50 mg
	(2) Lactose	34 mg
	(3) Corn starch	10.6 mg
	(4) Corn starch (paste)	5 mg
	(5) Magnesium stearate	0.4 mg
20	(6) Carboxymethylcellulose calcium	20 mg
	Total	120 mg

In accordance with a conventional manner, the above (1) to (6) are admixed and tableted using a tableting machine to give tablets.

25

Preparation Example 2

	(1) Compound obtained in Example 1	50 mg
	(2) Lactose	34 mg
	(3) Corn starch	10.6 mg
30	(4) Corn starch (paste)	5 mg
	(5) Magnesium stearate	0.4 mg
	(6) Carboxymethylcellulose calcium	20 mg
	Total	120 mg

In accordance with a conventional manner, the above (1) to (6) are admixed and tableted using a tableting machine to give tablets.

5 Reference Example 1-1

Amplification of rat SLC-1 receptor cDNA by PCR method using rat-brain-originated cDNA

Reverse transcription reaction was done using random primer, with rat-brain-originated poly (A)⁺RNA (Clone Tech Co.) used as a template. Reagent from the TaKaRa RNA PCR ver. 2 kit was used for the reverse transcription reaction.

Next, using this reverse transcription product as a template, amplification was done by a PCR method using synthetic DNA primers with sequence numbers 1 and 2.

15 Synthetic DNA primer was constructed to amplify genes in the domain where genes are translated by receptor protein.

At that time, individual restriction enzyme recognition sequences were also added on the 5' side and 3' side of the gene, to add a nucleotide sequence on the 5' side of gene which recognized restriction enzyme Sal I, and to add a nucleotide sequence on the 3' side of the gene which recognized the restriction enzyme Spe I. The reactant was constituted of 5 μ l of cDNA template, 0.4 μ M of synthetic DNA primer, 0.25 mM of dNTPs, 0.5 μ l of Pfu (StrataGene Co.) DNA polymerase, and buffers attached to enzymes, with total reaction quantity set at 50 μ l.

A thermal cycler (Parkin Elmer Co.) was used to produce cycles for amplification. After heating at 94°C for 60 seconds, the cycle consisting of 94°C for 60 seconds, 60°C for 30 seconds, and 72°C for 150 seconds, was repeated 35 times, and finally reaction was conducted at 72°C for 10 minutes. After 0.8% agarose gel electrophoresis, the amplified products were confirmed by ethidium bromide dying.

35

Reference Example 1-2

Subcloning of PCR products into plasmid vector, and confirmation of an amplified cDNA sequence by decoding of a nucleotide sequence in an inserted cDNA portion

The reaction product after PCR conducted in Reference Example 1-1 was separated using 0.8% low-melting point agarose gel. After the band section was cut out using a razor, DNA was recovered by conducting fragmentation, phenol extraction, phenol-chloroform extraction and ethanol precipitation. The recovered DNA was subcloned on plasmid vector PCR-Script Amp SK(+) in accordance with prescription of the PCR-Script™ Amp SK(+) cloning kit (Stratagene Co.). After this was introduced into Escherichia coli XL-1 Blue (Stratagene Co.) by transformation, the clones with fragments of inserted cDNA were selected in LB agar culture medium containing ampicillin and X-gal. Only clones showing white color were separated using a sterilized toothpick, and transformant E. coli XL-1 Blue/rat SLC-1 was obtained.

Each clone was cultured overnight in LB culture medium containing ampicillin, and plasmid DNA was prepared using QIA prep8 mini prep (Qiagen). A portion of the prepared DNA was digested with Sal I and Spe I, and the size of the inserted receptor cDNA fragment was confirmed. Reactions to determine nucleotide sequences were carried out using a DyeDeoxy Terminator Cycle Sequence Kit (Parkin Elmer Co.), and decoded using a fluorescent light automatic sequencer. The sequences of the 3 clones obtained were analyzed, and it was confirmed that all of them match the reported gene sequence (Sequence number: 4) in which the Sal I recognition sequence is added on the 5' side and the Spe I recognition sequence is added on the 3' side of the cDNA sequence (Lakaye, B., et al., Biochim. Biophys. Acta, Vol. 1401, pp. 216-220 (1998), accession No. AF08650) coding rat SLC-1 protein (Sequence number: 3).

Reference Example 1-3

Preparation of CHO cells for rat SLC-1 expression

The full-length amino acid sequence of rat brain originated SLC-1, which was confirmed in Reference Example 1-2, was coded, and plasmid was prepared using a plasmid
5 Midi Kit (Qiagen) from the E. coli transformed by the plasmid, to which the gene with Sal I recognition sequence added to the 5' side and Spe I recognition sequence added to the 3' side, had been introduced. Then, the insert
10 section was cut out by digesting with Sal I and Spe I. The insert DNA was cut out with a razor from the agarose gel after electrophoresis.

Next, fragmentation, phenol extraction, phenol-chloroform extraction, and ethanol precipitation, were conducted and the DNA was recovered. This insert DNA was
15 added to vector plasmid pAKKO-111H (the same vector plasmid as pAKKO1.11H described in Hinuma, S., et al., Biochim. Biophys. Acta, Vol. 1219, pp. 251-259 (1994)) for animal cell expression which was digested with Sal I and Spe I, and ligation was conducted using T4 ligase (TaKaRa Shuzo),
20 to construct pAKKO-SLC-1 plasmid for protein expression.

After E. coli DH5 transformed by pAKKO-SLC-1 was cultured, pAKKO-SLC-1 plasmid DNA was prepared using a Plasmid Midi Kit (Qiagen). This was introduced into CHO dhfr⁻ cells in accordance with the attached protocol, using
25 a CellPfect Transfection Kit (Amersham Pharmacia Biotech Co.). A coprecipitating suspension of 10 µg of DNA and calcium phosphate was prepared, and this suspension was added to 10 cm Petri dishes in which 5×10^5 or 1×10^6 of CHO dhfr⁻ cells had been seeded 24 hours previously. After
30 these cells were cultured for 1 day in MEMa culture medium containing 10% fetal bovine serum, subculture was conducted, and cultivation was conducted in selective culture medium, MEMa culture medium containing no nucleic acid but containing 10% dialyzed fetal bovine serum. 56
35 clones of colonies of the transformed CHO cells expressing SLC-1, proliferated in the selective culture medium, were

selected.

Reference Example 1-4

Selection of CHO/SLC-1 cell strain expressing a large
5 quantity of full-length rat SLC-1 receptor protein mRNA

The quantity of expressed full-length rat SLC-1
receptor protein mRNA of 56 clones of the CHO/SLC-1 strains
established in Reference Example 1-3, was measured using
a Cytostar T Plate (Amersham Pharmacia Biotech Co.) as shown
10 below according to the attached protocol. Each well of the
Cytostar T Plate was seeded with each clone of the CHO/SLC-1
strain by 2.5×10^4 , and cultured for 24 hours, then the
cells were fixed using 10% formalin. After 0.25% Triton
X-100 was added to each well to increase cell permeability,
15 ³⁵S-labeled riboprobes with sequence number: 5 were added
and hybridized. 20 mg/ml of RNaseA was added to each well
to digest free riboprobes. After the plate was thoroughly
washed, the radioactivity of the hybridized riboprobes was
determined using a Topcounter. Strains with high
20 radioactivity showed large amounts of mRNA expression. In
particular, mainly used was Clone number 44 among 3 clones
which showed large amounts of mRNA expression.

Reference Example 1-5

25 Isolation of plasmid containing human SLC-1 cDNA

After nicks were inserted into the DNA of Human fetal
brain originated cDNA library (SUPERScript™ cDNA Library;
GIBCOBRL Co.) according to the manual of the Genetrapp
cDNA positive selection system (GIBCOBRL Co.), using phage
30 F1 endonuclease, single stranded human fetal brain
originated cDNA library was prepared by digesting the
above-mentioned library with Escherichia coli exonuclease
III.

Biotin-14-dCTP was added to the 3' end of synthetic
35 oligonucleotide (equivalent to 1434-1451 of accession No.
U71092), sequence number: 6 which was prepared according

to the report by Kolakowski Jr., et al. (Kolakowski Jr., et al. (1996) FEBS Lett. Vol. 398, pp. 253-258) using Terminal Deoxynucleotidyl Transferase, and biotinated oligonucleotide was prepared. The above manual was followed regarding composition of a reaction mixture and reaction time.

After 4 µg of single stranded human fetal brain originated cDNA library was kept at 95°C for 1 minute, the library was rapidly cooled on ice. 20 ng of biotinated oligonucleotide was added, which was hybridized using the attached hybridization buffer at 37°C for 1 hour. Streptoavidin beads were added to the mixture, then single stranded human fetal brain originated cDNA hybridized by biotinated oligonucleotide, was isolated using a MAGNA-SEP Magnetic Particle Separator (GIBCOBRL Co.). The complementary strand was synthesized according to the manual, using as primer 50 ng of synthetic oligonucleotide (equivalent to 1011 - 1028 of accession No. U71092) of sequence number: 7, prepared based on the report by Kolakowski Jr., et al (Kolakowski Jr., et al. (1996) FEBS Lett. Vol. 398, pp. 253-258), to give the double stranded plasmid.

Reference Example 1-6

Determination of nucleotide sequence of plasmid containing isolated human SLC-1 cDNA

After the plasmid obtained in Reference Example 1-5 was introduced into ELECTROMAX™DH10B™ Cells by the electroporation method, clones with cDNA inserted fragments were selected in LB agar culture medium containing ampicillin and X-gal. Using a sterilized toothpick, only the clones showing white color were separated to give transformant E. coli DH10B/hSLC-1. Individual clones were cultured overnight in LB culture medium containing ampicillin, and the plasmid DNA was refined using QIA prep8 mini prep (Qiagen). The reactions

to determine nucleotide sequence were conducted using a DyeDeoxy Terminator Cycle Sequence Kit (Parkin Elmer Co.), and the nucleotide sequence was decoded using a fluorescent light automatic sequencer.

5 As the results, obtained was the sequence shown in Sequence number: 8. The amino acid sequence (Sequence number: 9) coded by the nucleotide sequence obtained here, differs from the human SLC-1 amino acid sequence predicted as the sequence analogized from rat SLC-1 based on human
10 chromosome DNA sequence (accession number: Z86090) containing human SLC-1 sequence, in the report by Lakaye, et al. (Lakaye, B., et al. (1998) *Biochim. Biophys. Acta*. Vol. 1401, pp. 216-220). This shows the presence of ATG, the initiation codon, on mRNA, in the 69 and 64 amino acids
15 upstream from the estimated sequence. *Escherichia coli* DH10B/phSLC1L8, the transformant produced by the plasmid containing DNA coding this sequence was deposited at IFO and NIBH.

20 Reference Example 1-7

Amplification of human SLC-1cDNA by PCR method using human fetal brain originated cDNA

Amplification by the PCR method was conducted using as the template plasmid containing human SLC-1 DNA sequence
25 cloned by the gene trap method, and using synthetic DNA primers of sequence number: 10 and sequence number: 11, and synthetic DNA primers of sequence number: 12 and sequence number: 13, respectively. The former amplified DNA and the latter amplified DNA were named as "human SLC-1(S)" and
30 "human SLC-1(L)", respectively. The synthetic DNA primer was constructed so that the genes in the domain translated to the receptor protein were amplified. At that time, a recognition sequence for each restriction enzyme was added on the 5' side and 3' side, so that the nucleotide sequence
35 recognized by restriction enzyme Sal I would be added on the 5' side of the gene, and the nucleotide sequence

recognized by restriction enzyme Spe I would be added on the 3' side. The composition of the reaction mixture for human SLC-1(S) amplification was: 5 µl of plasmid template containing human SLC-1 DNA sequence, 0.4 µM of respective synthetic DNA primers, 0.2 mM of dNTPs and 0.5 µl of Pfu DNA polymerase and buffers attached to the enzyme, with total quantity for reaction set at 50 µl. A thermal cycler (Parkin Elmer Co.) was used for the cycles for amplification. After heating at 94°C for 60 seconds, the cycle consisting of 94°C for 60 seconds, 57°C for 60 seconds, and 72°C for 150 seconds, was repeated 25 times, and finally the temperature of the reactant was maintained at 72°C for 10 minutes. The composition of the reaction mixture for human SLC-1(L) amplification was 5 µl of plasmid template containing human SLC-1 DNA sequence, 0.4 µM of respective synthetic DNA primers, 0.2 mM of dNTPs, 0.5 µl of Pfu DNA polymerase and buffers attached to the enzymes, with total quantity for reaction set at 50 µl. A thermal cycler (Parkin Elmer Co.) was used for the cycles for amplification. After heating at 94°C for 60 seconds, the cycle consisting of 94°C for 60 seconds, 60°C for 60 seconds, and 72°C for 3 minutes, was repeated 25 times, and finally the temperature of the reactant was maintained at 72°C for 10 minutes. After 0.8% agarose gel electrophoresis, confirmation of amplified products was conducted by ethidium bromide dying.

Reference Example 1-8

Subcloning of PCR product into plasmid vector and confirmation of amplified cDNA sequence by decoding of nucleotide sequence of inserted cDNA section

The reaction product after PCR in Reference Example 1-7 was separated using 0.8% low-melting point agarose gel, and the band section was cut out using a razor. After that, fragmentation, phenol extraction, phenol-chloroform extraction, and ethanol precipitation were conducted, and

the DNA was recovered. The recovered DNA was subcloned into pCR-Script Amp SK(+) plasmid vector, as prescribed by the PCR-Script™ Amp SK(+) cloning kit (Stratagene Co.). After this was introduced into Escherichia coli DH5a competent cells (TOYOB0) and transformed, the clones with cDNA inserted fragments were selected in LB agar culture medium containing ampicillin and X-gal. Using a sterilized toothpick, only clones showing white color were separated to give E. coli DH5α/hSLC-1(S), which is a transformant of human SLC-1 (S), and E. coli DH5α/hSLC-1(L), which is a transformant of human SLC-1 (L). Each clone was cultured overnight in LB culture medium containing ampicillin, and plasmid DNA was prepared using QIA prep8 mini prep (Qiagen). Some of the prepared DNA was digested with Sal I and Spe I restriction enzymes, and the size of the receptor cDNA fragments inserted was confirmed. The reactions to determine nucleotide sequence were conducted using a DyeDeoxy Terminator Cycle Sequence Kit (Parkin Elmer Co.) and the nucleotide sequence was decoded using a fluorescent light automatic sequencer. The sequence of the obtained clones respectively matched the DNA sequence (sequence number:14) which should be amplified by synthetic DNA primers of sequence number: 10 and sequence number: 11 using human SLC-1 gene as a template, and the DNA sequence (sequence number: 15) which should be amplified by synthetic DNA primers of sequence number: 12 and sequence number: 13 using human SLC-1 gene as a template.

Reference Example 1-9

Preparation of CHO cells for expression of human SLC-1(S), and CHO cells for expression of human SLC-1(L)

Plasmid was prepared from the E. coli clones transformed by the plasmid wherein inserted were human SLC-1(S) and human SLC-1(L) whose sequences were confirmed in Reference Example 1-8, using a Plasmid Midi Kit (Qiagen), and the insert section was cut out using Sal I and Spe I

restriction enzymes. After electrophoresis was conducted, the insert DNA was cut out from agarose gel using a razor. Next, fragmentation, phenol extraction, phenol-chloroform extraction, and ethanol precipitation were conducted, and the insert DNA was recovered.

This insert DNA was added to pAKKO-111H vector plasmid for animal cell expression, digested with Sal I and Spe I (the same vector plasmid as the pAKKO1.11H described in Hinuma, S., et al., Biochim. Biophys. Acta, Vol. 1219, pp. 251-259 (1994)), and ligation was conducted by adding T4 ligase (TaKaRa Shuzo), to construct pAKKO-hSLC-1(S) and pAKKO-hSLC-1(L) plasmids for protein expression.

After E. coli DH5 α (TOYOBO) transformed by pAKKO-hSLC-1(S) and pAKKO-hSLC-1(L) was cultured, pAKKO-hSLC-1(S) and pAKKO-hSLC-1(L) plasmid DNAs were prepared using a Plasmid Midi Kit (Qiagen). These were introduced into CHO dhfr⁻ cells in accordance with the attached protocol, using a CellPfect Transfection Kit (Amersham Pharmacia Biotech Co.). A coprecipitative suspension of 10 μ g of DNA with calcium phosphate was made, which was added to 10 cm Petri dishes seeded 24 hours in advance with 5×10^5 or 1×10^6 CHO dhfr⁻ cells. After the above was cultured for 1 day in MEM α culture medium containing 10% fetal bovine serum, subculture was conducted, and then cultivation was conducted in MEM α culture medium containing no nucleic acid but containing 10% dialyzed fetal bovine serum, which is a selective culture medium. 56 clones of colonies of transformed cells which are human SLC-1(S) gene introduced CHO cells, and 61 clones of colonies of transformed cells which are human SLC-1(L) gene introduced CHO cells, both of which proliferated in the selective culture medium, were selected.

Reference Example 1-10

Selection of cell colonies into which genes with large quantities of human SLC-1(S) and human SLC-1 (L) mRNA

expression have been introduced

The quantities of expressed mRNA of 56 clones of CHO/hSLC-1(S) colonies and 61 clones of CHO/hSLC-1(L) colonies, both of which were established in Reference Example 1-9, were measured in accordance with the attached protocol using a Cytostar T Plate (Amersham Pharmacia Biotech Co.) as shown below.

After each well of the Cytostar T Plate was seeded with each clone of CHO/hSLC-1(S) colonies and CHO/hSLC-1(L) colonies by 2.5×10^4 , and cultured for 24 hours, the cells were fixed using 10% formalin.

After 0.25% Triton X-100 was added to each well to increase cell permeability, ^{35}S -labeled riboprobe of sequence number: 16 was added and hybridization was conducted.

20 mg/ml of RNaseA was added to each well to digest free riboprobe. After the plate was washed well, the radioactivity of the hybridized riboprobe was determined. Colonies showing high radioactivity expressed large quantities of mRNA. Of the 7 clones which expressed large quantities of mRNA, mainly used was Clone number 57.

Experimental Example 1

Determination of antagonist activity using GTPgS binding assay of test compound

Membrane fraction was prepared by the following method, using the human SLC-1 expressing CHO cell clone 57 obtained in Reference Example 1-10, and the rat SLC-1 expressing CHO cell clone 44 obtained in Reference Example 1-4.

The human and rat SLC-1 expressing CHO cells (1×10^8) were scraped in buffer saline phosphate (pH 7.4) to which 5 mM EDTA (ethylenediaminetetraacetic acid) had been added, and centrifuged. 10 ml of homogenized buffer (10 mM NaHCO_3 , 5 mM EDTA, pH 7.5) was added to the cell pellets, and they were homogenized using a Polytron homogenizer. The

supernatant obtained by centrifugation at $400 \times g$ for 15 minutes was further centrifuged at $100,000 \times g$ for 1 hour, to obtain the membrane fraction precipitate. This precipitate was suspended in 2 ml of assay buffer [50 mM
5 Tris-HCl(pH 7.5), 1 mM EDTA, 0.1% BSA (bovine serum albumin), 10 mM $MgCl_2$, 100 mM NaCl, 1 μM GDP (guanosine 5'-diphosphate), 0.25 mM PMSF (phenylmethylsulfonyl fluoride), 1 mg/ml pepstatin, 20 mg/ml leupeptin, 10 mg/ml phosphoramidon], which was centrifuged at $100,000 \times g$ for
10 1 hour. The membrane fraction recovered as precipitate was suspended again in 2 ml of assay buffer, and after the suspension was divided, individual portions were preserved at $-80^\circ C$ and thawed before every use.

Determination of antagonist activity of the test
15 compound was conducted as shown below. After 171 μl of SLC-1 expressing CHO cell membrane fractions diluted with assay buffer was poured into each well of a 96-well polypropylene plate, 2 μl of $3 \times 10^{-10} M$ MCH diluted with DMSO solution, 2 μl of test compound solution diluted to various
20 concentrations, and 25 μl of [^{35}S]-Guanosine 5'-(γ -thio) triphosphate (produced by Daiichi Kagaku Yakuhin) were added respectively. (Final concentration of cell membrane: 20 $\mu g/ml$, final concentration of [^{35}S]-Guanosine 5'-(γ -thio) triphosphate: 0.33 nM).

25 After this reaction mixture was allowed to react for 1 hour under stirring, it was filtered under vacuum using a glass filter (GF-C), then the filter was washed 3 times with 300 μl of washing solution (50 mM Tris-HCl buffer solution pH 7.5). 50 ml of liquid scintillator was added
30 to the glass filter, and residual radioactivity was determined using a liquid scintillation counter.

The IC_{50} value of the compound was calculated from the binding inhibition rate (%), based on the definition that the binding inhibition rate (%) = (radioactivity when
35 compound and MCH were added - radioactivity when DMSO solution was added)/(radioactivity when MCH was added -

radioactivity when DMSO solution was added) $\times 100$.

The results were shown below.

Compound Number	Inhibition Activity (IC ₅₀ value: nM)
Reference Example 25	90
Example 1	40

5

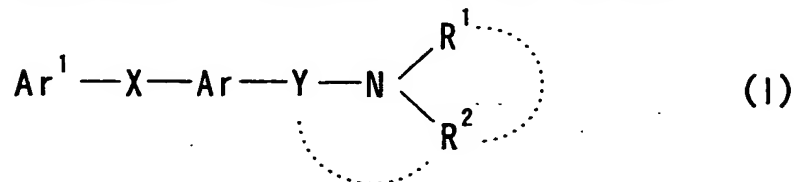
Industrial Applicability

Compounds (I), (I') and salts thereof possess excellent MCH receptor antagonistic activities, and are useful as an agent for preventing or treating obesity, etc.

10

CLAIMS

1. A melanin-concentrating hormone antagonist which comprises a compound of the formula :



- 5 wherein Ar¹ is a cyclic group which may have substituents;
 X is a spacer having a main chain of 1 to 6 atoms;
 Y is a bond or a spacer having a main chain of 1 to 6 atoms;
 Ar is a monocyclic aromatic ring which may be condensed with
 10 a 4 to 8 membered non-aromatic ring, and may have further substituents;
 R¹ and R² are independently hydrogen atom or a hydrocarbon group which may have substituents; R¹ and R², together with the adjacent nitrogen atom, may form a nitrogen-containing
 15 hetero ring which may have substituents; R² may form a spiro ring together with Ar; or R², together with the adjacent nitrogen atom and Y, may form a nitrogen-containing hetero ring which may have substituents; or a salt thereof.
- 20 2. An antagonist according to claim 1, wherein Y is a spacer having a main chain of 1 to 6 atoms; R¹ and R² are independently hydrogen atom or a hydrocarbon group which may have substituents; R¹ and R², together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring
 25 which may have substituents; or R² may form a spiro ring together with Ar.
3. An antagonist according to claim 2, wherein Ar¹ is an aromatic group which may have substituents; and "a hydrocarbon group which may have substituents" for R¹ and
 30 R² is "C₁₋₆ alkyl which may have substituents".
4. An antagonist according to claim 1, wherein the cyclic

group for Ar¹ is C₆₋₁₄ monocyclic or condensed polycyclic aromatic hydrocarbon group.

5 5. An antagonist according to claim 1, wherein the cyclic group for Ar¹ is a group formed by removing an optional one hydrogen atom from an aromatic ring assemble in which 2 or 3 C₆₋₁₄ monocyclic or condensed polycyclic aromatic hydrocarbon groups are directly bonded by single bonds.

10 6. An antagonist according to claim 1, wherein the cyclic group for Ar¹ is a group formed by removing an optional one hydrogen atom from an aromatic ring assemble in which C₆₋₁₄ monocyclic or condensed polycyclic aromatic hydrocarbon and 5 to 10 membered aromatic hetero ring are directly
15 bonded by a single bond.

7. An antagonist according to claim 1, wherein Ar¹ is phenyl, biphenyl, phenyl-pyridyl, phenyl-furyl, phenyl-isoxazolyl, diphenyl-oxazolyl, pyridyl-phenyl,
20 phenyl-pyrimidinyl, benzofuranyl-phenyl, furyl-phenyl, terphenyl, thienyl-phenyl, indolyl, naphthyl-oxadiazolyl, benzofuranyl-oxadiazolyl, benzothienyl, benzofuranyl, fluorenyl, pyridyl-pyrrolyl or thioxanthanyl;
25 each of which may have 1 to 3 substituents selected from the group consisting of halogen atom; nitro; C₁₋₃ alkylenedioxy; optionally halogenated C₁₋₆ alkyl; hydroxy-C₁₋₆ alkyl; optionally halogenated C₃₋₆ cycloalkyl; optionally halogenated C₁₋₆ alkoxy; optionally halogenated
30 C₁₋₆ alkythio; hydroxy; C₇₋₁₉ aralkyloxy which may have substituents; C₆₋₁₄ aryloxy which may have substituents; amino; mono-C₁₋₆ alkylamino; di-C₁₋₆ alkylamino; 5 to 7 membered saturated cyclic amino which may have substituents and may be condensed with a benzene ring; 5 to 7 membered
35 non-aromatic heterocyclic groups which may have substituents; formyl; carboxy; C₆₋₁₄ aryl-carbonyl which may

have substituents; C₆₋₁₄ aryl-carbamoyl which may have substituents; aromatic hetero ring-carbamoyl which may have substituents; C₁₋₆ alkoxy-carbonyl; optionally halogenated C₁₋₆ alkyl-carboxamide; C₆₋₁₄ aryl-carboxamide
5 which may have substituents; C₇₋₁₉ aralkyl-carboxamide which may have substituents; aromatic hetero ring-carboxamide which may have substituents; N-(C₆₋₁₄ aryl-carbonyl which may have substituents)-N-C₁₋₆ alkylamino; C₆₋₁₄ arylamino-carbonylamino which may have substituents; C₆₋₁₄
10 arylsulfonylamino which may have substituents; C₆₋₁₄ aryl-carbonyloxy which may have substituents; oxo; carboxy-C₁₋₆ alkyl; C₁₋₆ alkoxy-carbonyl-C₁₋₆ alkyl; C₇₋₁₉ aralkyl which may have substituents; aromatic hetero ring-C₁₋₆ alkoxy; and cyano.

15
8. An antagonist according to claim 1, wherein Ar¹ is piperidinyl, piperazinyl, pyrrolidinyl, dihydropyridyl or tetrahydropyridyl; each of which may have 1 or 2 substituents selected from the group consisting of oxo, C₆₋₁₄
20 aryl which may have substituents, hydroxy, C₇₋₁₉ aralkyloxy-carbonyl, and C₇₋₁₉ aralkyl.

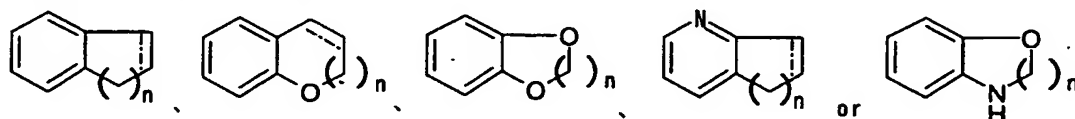
9. An antagonist according to claim 1, wherein the "spacer having a main chain of 1 to 6 atoms" for X and Y
25 is a bivalent group consisting of 1 to 3 species selected from -O-, -S-, -CO-, -SO-, -SO₂-, -NR⁸- (R⁸ is hydrogen atom, optionally halogenated C₁₋₆ alkyl, optionally halogenated C₁₋₆ alkyl-carbonyl, optionally halogenated C₁₋₆ alkylsulfonyl), and a bivalent C₁₋₆ non-cyclic hydrocarbon
30 group which may have substituents.

10. An antagonist according to claim 1, wherein X is -CONR^{8c}-, -NR^{8c}CO-, -CH=CH-CONR^{8c}- or -SO₂NR^{8c}-
wherein R^{8c} is hydrogen atom or C₁₋₆ alkyl.

35
11. An antagonist according to claim 1, wherein Y is an

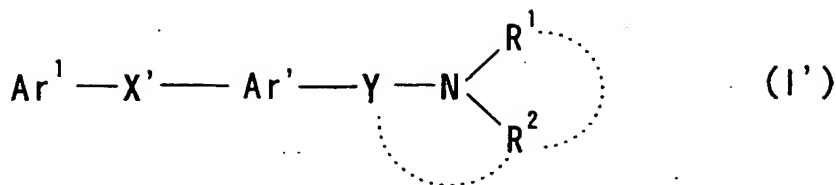
optionally halogenated bivalent C_{1-6} non-cyclic hydrocarbon group.

12. An antagonist according to claim 1, wherein Ar is a ring of the formula :

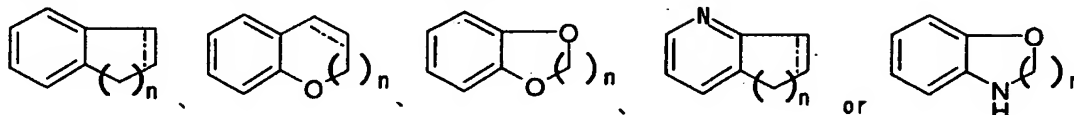


wherein ----- is a single bond or double bond, n is an integer of 1 to 4.

13. An antagonist according to claim 1, wherein R^1 and R^2 are hydrogen atom or C_{1-6} alkyl which may have substituents; or R^1 and R^2 , together with the adjacent nitrogen atom, form a 3 to 8 membered nitrogen-containing hetero ring.
14. An antagonist according to claim 1, which is an agent for preventing or treating diseases caused by a melanin-concentrating hormone.
15. An antagonist according to claim 1, which is an agent for preventing or treating obesity.
16. An antagonist according to claim 1, which is an anorectic agent.
17. A pharmaceutical, which comprises a melanin-concentrating hormone antagonist in combination with at least one species selected from the group consisting of an agent for treating diabetes, an agent for treating hypertension and an agent for treating arteriosclerosis.
18. A compound of the formula :



wherein Ar^1 is a cyclic group which may have substituents;
 Ar' is a ring of the formula :



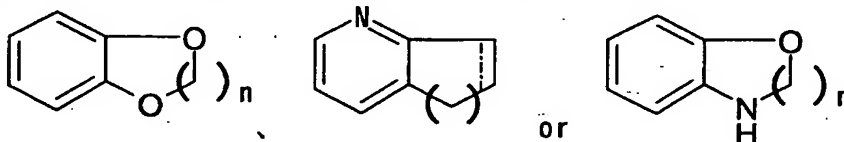
5 wherein ----- is a single bond or double bond, n is an integer of 1 to 4, and each ring may have substituents;

X' is $-\text{CONR}^{\text{sc}}-$, $-\text{NR}^{\text{sc}}\text{CO}-$, $-\text{CH}=\text{CH}-\text{CONR}^{\text{sc}}-$ or $-\text{SO}_2\text{NR}^{\text{sc}}-$ where R^{sc} is hydrogen atom or C_{1-6} alkyl;

Y is a spacer having a main chain of 1 to 6 atoms;

10 R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2 , together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; or R^2 , together with the adjacent nitrogen atom and Y , may form a
 15 nitrogen-containing hetero ring which may have substituents;

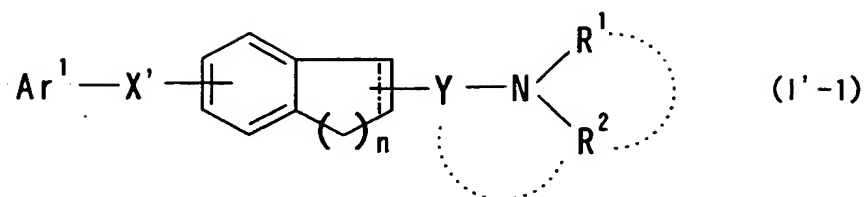
provided that Ar' is a ring of the formula :



wherein symbols have the same meanings as defined above,
 20 and each ring may have substituents, when X' is $-\text{SO}_2\text{NH}-$; and provided that Ar^1 is not biphenyl which may be substituted, when X' is $-\text{CONH}-$ and Ar' is any one of benzopyran, dihydrobenzopyran, dihydrobenzoxazine, dihydrobenzoxazole or tetrahydrobenzoxazepine;
 25 (excluding N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]-4-biphenylcarboxamide); or a salt thereof.

19. A compound of the formula :

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wherein Ar¹ is a cyclic group which may have substituents;

----- is a single bond or double bond;

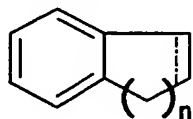
n is an integer of 1 to 4;

5 X' is -CONR^{8c}-, -NR^{8c}CO- or -CH=CH-CONR^{8c}- where R^{8c} is hydrogen atom or C₁₋₆ alkyl;

Y is a spacer having a main chain of 1 to 6 atoms;

R¹ and R² are independently hydrogen atom or a hydrocarbon group which may have substituents; R¹ and R², together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; or R², together with the adjacent nitrogen atom and Y, may form a nitrogen-containing hetero ring which may have substituents;

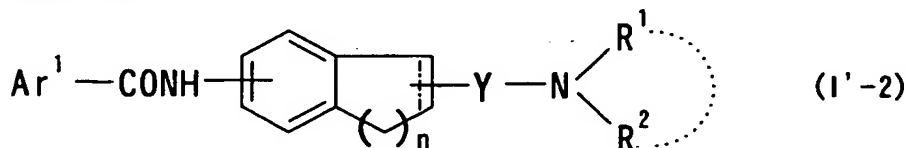
15 a ring of the formula :



wherein symbols have the same meanings as defined above, may have further substituents;

provided that N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]-4-biphenylcarboxamide is excluded; or a salt thereof.

20. A compound according to claim 19, which is of the formula :

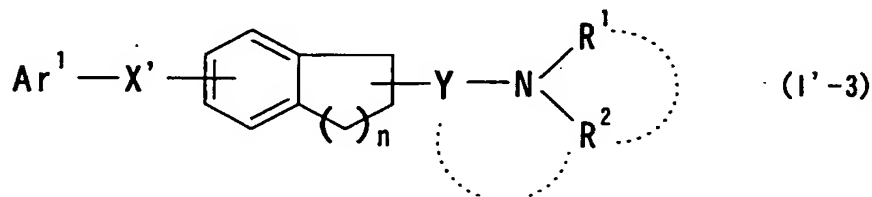


25 wherein R¹ and R² are independently hydrogen atom or a hydrocarbon group which may have substituents; R¹ and R²,

together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; the other symbols have the same meanings as defined in claim 19.

21. A compound according to claim 20, wherein Ar^1 is an aromatic group which may have substituents; and "a hydrocarbon group which may have substituents" for R^1 and R^2 is " C_{1-6} alkyl which may have substituents".

22. A compound of the formula :



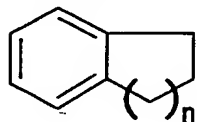
wherein Ar^1 is a cyclic group which may have substituents; n is an integer of 1 to 4;

15 X' is $-CONR^{8c}-$, $-NR^{8c}CO-$ or $-CH=CH-CONR^{8c}-$ where R^{8c} is hydrogen atom or C_{1-6} alkyl;

Y is a spacer having a main chain of 1 to 6 atoms;

R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2 , together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; or R^2 , together with the adjacent nitrogen atom and Y , may form a nitrogen-containing hetero ring which may have substituents;

25 a ring of the formula :



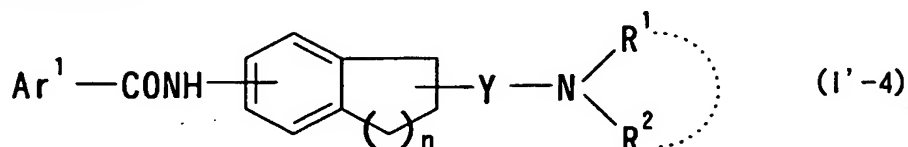
wherein n has the same meaning as defined above, may have further substituents;

provided that N-[2-(N,N-dimethylamino)methyl-6-

30 tetralinyl]-4-biphenylcarboxamide is excluded; or a salt

thereof.

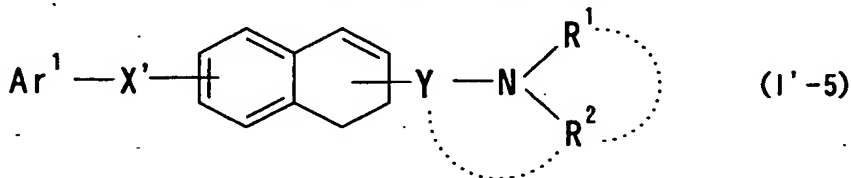
23. A compound according to claim 22, which is of the formula :



wherein R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2 , together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; the other symbols have the same meanings as defined in claim 22.

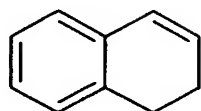
24. A compound according to claim 23, wherein Ar^1 is an aromatic group which may have substituents; and "a hydrocarbon group which may have substituents" for R^1 and R^2 is "C₁₋₆ alkyl which may have substituents".

25. A compound of the formula :



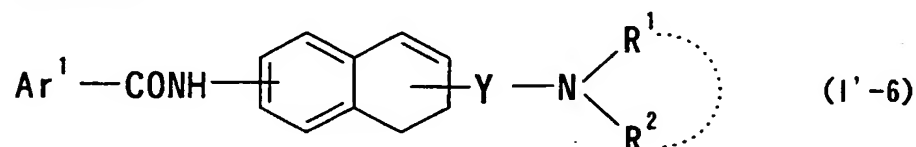
wherein Ar^1 is a cyclic group which may have substituents; X' is $-\text{CONR}^{\text{sc}}-$, $-\text{NR}^{\text{sc}}\text{CO}-$ or $-\text{CH}=\text{CH}-\text{CONR}^{\text{sc}}-$ where R^{sc} is hydrogen atom or C₁₋₆ alkyl; Y is a spacer having a main chain of 1 to 6 atoms; R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2 , together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; or R^2 , together with the adjacent nitrogen atom and Y , may form a nitrogen-containing hetero ring which may have substituents;

a ring of the formula :



may have further substituents; or a salt thereof.

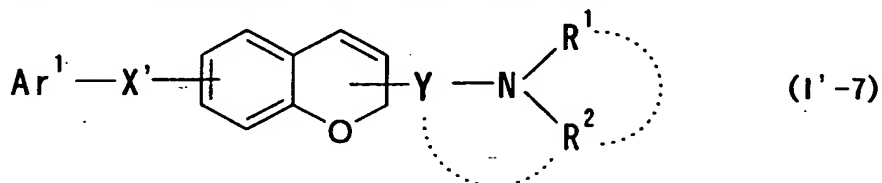
- 5 26. A compound according to claim 25, which is of the formula :



- 10 wherein R¹ and R² are independently hydrogen atom or a hydrocarbon group which may have substituents; R¹ and R², together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; the other symbols have the same meanings as defined in claim 25.

- 15 27. A compound according to claim 26, wherein Ar¹ is an aromatic group which may have substituents; and "a hydrocarbon group which may have substituents" for R¹ and R² is "C₁₋₆ alkyl which may have substituents".

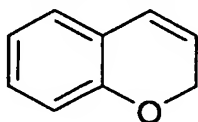
- 20 28. A compound of the formula :



- wherein Ar¹ is a cyclic group which may have substituents; X' is -CONR^{8c}-, -NR^{8c}CO-, -CH=CH-CONR^{8c}- or -SO₂NR^{8c}- where R^{8c} is hydrogen atom or C₁₋₆ alkyl;
- 25 Y is a spacer having a main chain of 1 to 6 atoms; R¹ and R² are independently hydrogen atom or a hydrocarbon group which may have substituents; R¹ and R², together with the adjacent nitrogen atom, may form a nitrogen-containing

hetero ring which may have substituents; or R^2 , together with the adjacent nitrogen atom and Y, may form a nitrogen-containing hetero ring which may have substituents;

5 a ring of the formula :

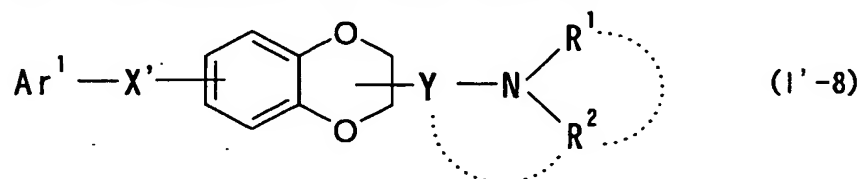


may have further substituents;

provided that Ar^1 is not biphenyl which may be substituted, when X' is $-CONH-$; or a salt thereof.

10

29. A compound of the formula :



wherein Ar^1 is a cyclic group which may have substituents; X' is $-CONR^{8c}-$, $-NR^{8c}CO-$, $-CH=CH-CONR^{8c}-$ or $-SO_2NR^{8c}-$ where R^{8c} is hydrogen atom or C_{1-6} alkyl;

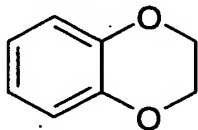
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Y is a spacer having a main chain of 1 to 6 atoms;

R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2 , together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; or R^2 , together with the adjacent nitrogen atom and Y, may form a nitrogen-containing hetero ring which may have substituents;

20

a ring of the formula :

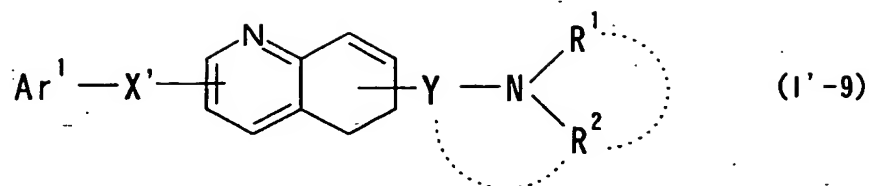


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may have further substituents; or a salt thereof.

30. A compound of the formula :

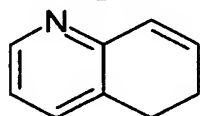
346



wherein Ar¹ is a cyclic group which may have substituents;
 X' is -CONR^{8c}-, -NR^{8c}CO-, -CH=CH-CONR^{8c}- or -SO₂NR^{8c}- where
 R^{8c} is hydrogen atom or C₁₋₆ alkyl;

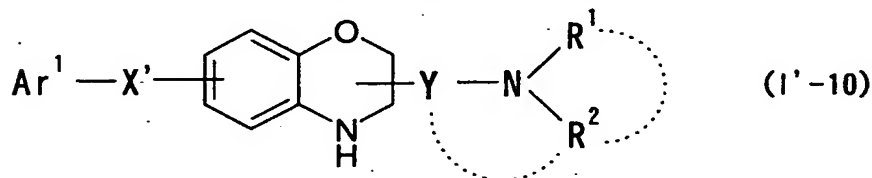
- 5 Y is a spacer having a main chain of 1 to 6 atoms;
 R¹ and R² are independently hydrogen atom or a hydrocarbon
 group which may have substituents; R¹ and R², together with
 the adjacent nitrogen atom, may form a nitrogen-containing
 hetero ring which may have substituents; or R², together
 10 with the adjacent nitrogen atom and Y, may form a
 nitrogen-containing hetero ring which may have
 substituents;

a ring of the formula :



- 15 may have further substituents; or a salt thereof.

31. A compound of the formula :

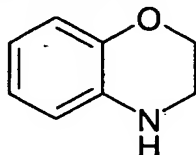


wherein Ar¹ is a cyclic group which may have substituents;
 20 X' is -CONR^{8c}-, -NR^{8c}CO-, -CH=CH-CONR^{8c}- or -SO₂NR^{8c}- where
 R^{8c} is hydrogen atom or C₁₋₆ alkyl;

- Y is a spacer having a main chain of 1 to 6 atoms;
 R¹ and R² are independently hydrogen atom or a hydrocarbon
 group which may have substituents; R¹ and R², together with
 25 the adjacent nitrogen atom, may form a nitrogen-containing
 hetero ring which may have substituents; or R², together
 with the adjacent nitrogen atom and Y, may form a
 nitrogen-containing hetero ring which may have

substituents;

a ring of the formula :



may have further substituents;

- 5 provided that Ar¹ is not biphenyl which may be substituted, when X' is -CONH-; or a salt thereof.

32. A pharmaceutical composition which comprises a compound as defined in any one of claims 18, 19, 22, 25,
10 26, 28, 29, 30 and 31.

33. A prodrug of a compound as defined in any one of claims 18, 19, 22, 25, 26, 28, 29, 30 and 31.

- 15 34. A compound according to claim 18, which is
N-[2-(N,N-dimethylamino)methyl-6-tetralinyl]-(4'-methoxybiphenyl-4-yl)carboxamide;
4'-fluoro-N-[6-[(N,N-dimethylamino)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide;
20 4'-fluoro-N-[6-(1-piperidinylmethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide;
4'-fluoro-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide;
25 (+)-4'-fluoro-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide;
(-)-4'-fluoro-N-[6-[(N,N-dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide;
30 4'-chloro-N-[3-[(N,N-dimethylamino)methyl]-2H-chromen-7-yl][1,1'-biphenyl]-4-carboxamide;
4'-fluoro-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-

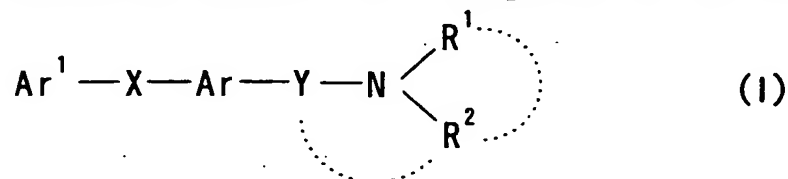
- naphthalenyl][1,1'-biphenyl]-4-carboxamide;
N-[3-[(dimethylamino)methyl]-2H-chromen-7-yl]-4'-
fluoro[1,1'-biphenyl]-4-carboxamide;
4'-chloro-N-[6-[(dimethylamino)methyl]-5-methyl-7,8-
5 dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide;
6-(4-methoxyphenyl)-N-[5-methyl-6-(1-
pyrrolidinylmethyl)-7,8-dihydro-2-
naphthalenyl]nicotinamide;
4'-chloro-N-[7-[(dimethylamino)methyl]-5,6-dihydro-3-
10 quinolinyl][1,1'-biphenyl]-4-carboxamide;
4-(4-chlorophenyl)-N-[6-(1-pyrrolidinylmethyl)-7,8-
dihydro-2-naphthalenyl]-3,6-dihydro-1(2H)-
pyridinecarboxamide;
N-[6-[(dimethylamino)methyl]-7,8-dihydro-2-
15 naphthalenyl]-4-(4-fluorophenyl)-1-
piperidinecarboxamide;
4-(4-methoxyphenyl)-N-[6-(1-pyrrolidinylmethyl)-5-
methyl-7,8-dihydro-2-naphthalenyl]-1-
piperidinecarboxamide;
20 4'-fluoro-N-[6-[2-(1-pyrrolidinyl)ethyl]-7,8-dihydro-2-
naphthalenyl][1,1'-biphenyl]-4-carboxamide;
4'-chloro-N-[6-[2-(1-pyrrolidinyl)ethyl]-7,8-dihydro-2-
naphthalenyl][1,1'-biphenyl]-4-carboxamide;
4'-chloro-N-[2-[(dimethylamino)methyl]-3,4-dihydro-2H-
25 1,4-benzoxazin-6-yl][1,1'-biphenyl]-4-carboxamide;
4-(4-methoxyphenyl)-N-[5-methyl-6-(1-
pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]-1-
piperidinecarboxamide;
4-(4-chlorophenyl)-N-[6-[(4-methyl-1-
30 piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl]-1-
piperidinecarboxamide;
4'-chloro-N-[2-[(dimethylamino)methyl]-1H-inden-6-
yl][1,1'-biphenyl]-4-carboxamide;
4'-fluoro-N-[2-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-
35 1,4-benzoxazin-6-yl][1,1'-biphenyl]-4-carboxamide;
4'-fluoro-N-[5-methyl-6-[(4-methyl-1-

piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide;

4'-chloro-N-[5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide; or

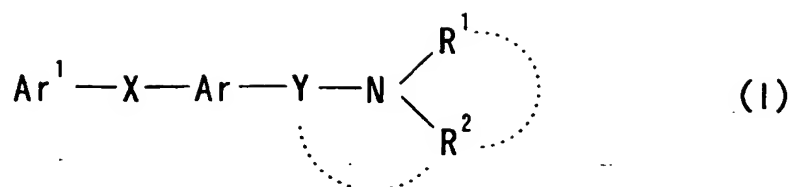
4-(4-chlorophenyl)-N-[5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide.

35. A method for preventing or treating diseases caused by a melanin-concentrating hormone in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of the formula :



- wherein Ar^1 is a cyclic group which may have substituents; X is a spacer having a main chain of 1 to 6 atoms; Y is a bond or a spacer having a main chain of 1 to 6 atoms; Ar is a monocyclic aromatic ring which may be condensed with a 4 to 8 membered non-aromatic ring, and may have further substituents; R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2 , together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; R^2 may form a spiro ring together with Ar; or R^2 , together with the adjacent nitrogen atom and Y, may form a nitrogen-containing hetero ring which may have substituents; or a salt thereof.

36. A method for preventing or treating obesity in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of the formula :



wherein Ar^1 is a cyclic group which may have substituents;
 X is a spacer having a main chain of 1 to 6 atoms;

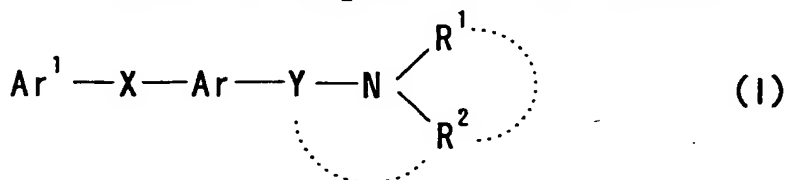
Y is a bond or a spacer having a main chain of 1 to 6 atoms;

5 Ar is a monocyclic aromatic ring which may be condensed with a 4 to 8 membered non-aromatic ring, and may have further substituents;

R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2 , together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; R^2 may form a spiro ring together with Ar ; or R^2 , together with the adjacent nitrogen atom and Y , may form a nitrogen-containing hetero ring which may have substituents; or a salt thereof.

15

37. Use of a compound of the formula :



wherein Ar^1 is a cyclic group which may have substituents;
 X is a spacer having a main chain of 1 to 6 atoms;

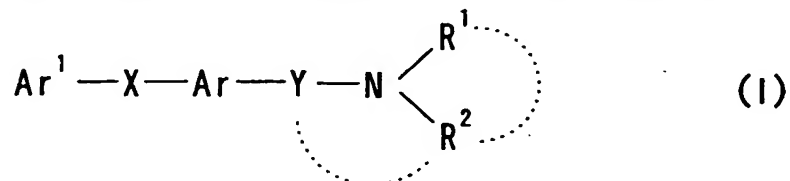
20 Y is a bond or a spacer having a main chain of 1 to 6 atoms;
 Ar is a monocyclic aromatic ring which may be condensed with a 4 to 8 membered non-aromatic ring, and may have further substituents;

R^1 and R^2 are independently hydrogen atom or a hydrocarbon group which may have substituents; R^1 and R^2 , together with the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; R^2 may form a spiro ring together with Ar ; or R^2 , together with the adjacent nitrogen atom and Y , may form a nitrogen-containing hetero ring which may have substituents; or a salt thereof;

30

for the manufacture of a pharmaceutical preparation for preventing or treating diseases caused by a melanin-concentrating hormone.

- 5 38. Use of a compound of the formula :



- wherein Ar¹ is a cyclic group which may have substituents;
 X is a spacer having a main chain of 1 to 6 atoms;
 Y is a bond or a spacer having a main chain of 1 to 6 atoms;
 10 Ar is a monocyclic aromatic ring which may be condensed with a 4 to 8 membered non-aromatic ring, and may have further substituents;
 R¹ and R² are independently hydrogen atom or a hydrocarbon group which may have substituents; R¹ and R², together with
 15 the adjacent nitrogen atom, may form a nitrogen-containing hetero ring which may have substituents; R² may form a spiro ring together with Ar; or R², together with the adjacent nitrogen atom and Y, may form a nitrogen-containing hetero ring which may have substituents; or a salt thereof;
 20 for the manufacture of a pharmaceutical preparation for preventing or treating obesity.

SEQUENCE LISTING

<110> Takeda Chemical Industries, Ltd.

<120> Melanin Concentrating Hormone Antagonist

<130> 2648W00P

<150> JP 11-266298

<151> 1999-09-20

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35 40 45

Thr Ile Cys Leu Leu Gly Ile Val Gly Asn Ser Thr Val Ile Phe Ala

50 55 60

Val Val Lys Lys Ser Lys Leu His Trp Cys Ser Asn Val Pro Asp Ile

65 70 75 80

Phe Ile Ile Asn Leu Ser Val Val Asp Leu Leu Phe Leu Leu Gly Met

85 90 95

Pro Phe Met Ile His Gln Leu Met Gly Asn Gly Val Trp His Phe Gly

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Phe Val Tyr Leu Tyr Asn Ala Ala Ile Ser Leu Gly Tyr Ala Asn Ser		
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 Thr Gly Thr Gly Trp MeT Asp Leu Glu Ala Ser Leu Leu Pro Thr Gly
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 Pro Asn Ala Ser Asn Thr Ser Asp Gly Pro Asp Asn Leu Thr Ser Ala
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7/11

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8/11

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10/11

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11/11

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